

Conversion from KADIAN® to the same total daily dose of other controlled-release morphine preparations may lead to either excessive sedation at peak serum concentrations or inadequate analgesia at trough serum concentrations. This is because the T_{max} may occur more rapidly and the C_{max} may be higher with the other preparation than with KADIAN®. These rapid and higher peak levels may be associated with increased side effects; therefore, close observation and appropriate dosage adjustments are recommended in this situation.

Selection of a KADIAN® Starting Dose

It is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior opioid analgesic treatment experience. In the selection of the initial dose of KADIAN®, attention should be given to

- the total daily dose, potency, and kind of opioid the patient has been taking previously;
- the reliability of the relative potency estimate used to calculate the equivalent dose of morphine needed;
- the patient's degree of opioid tolerance;
- the general condition and medical status of the patient;
- concurrent medication(s); and
- the type and severity of the patient's pain.

Conversion from other oral morphine to KADIAN®

Patients taking other oral morphine formulations may be converted to KADIAN® by totaling the daily dose of morphine and giving one-half of the total as daily dose KADIAN® capsules every 12 hours. The first dose of KADIAN® may be given with the last dose of conventional oral morphine because of the long delay until the peak effect after administration of KADIAN®. For example, if a patient had been previously taking a total of 60 mg of immediate-release morphine each day, the initial starting dose of KADIAN® could be 30 mg twice daily.

Equianalgesic Tables

Patients who have never been treated with opioids should be started on the low, recommended starting doses because these patients lack tolerance to opioids. However, patients who are already receiving opioids are likely to have developed tolerance and may experience insufficient pain relief and possibly withdrawal if adequate doses are not administered. Because opioids have different formulations and potencies, it is important to know what strengths of a new opioid drug are equal to the strength of the formulation that the patient is currently being treated with. For example, if a patient is taking 200mg of codeine a day, they might be started at the equivalent dose of morphine, 60mg, given as 30mg twice daily.

Multiple tables of oral and parenteral opioid equivalents are available for use to guide these conversions. These tables are called equianalgesic-dosing tables. Although the equianalgesic doses are equal in theory, in practice, there is variable cross-tolerance to opioids among individual patients. In addition, the ratios obtained from these tables are only approximate; therefore use caution when converting a patient from one opioid or one dosage form to another. It may be advisable to initiate the dose of the converted opioid at 50% of the first opioid to avoid excessive side effects unless a patient is in severe pain.

There are several methods to help you convert from one opioid drug or dosage form to another. Because there are several ways to calculate an equianalgesic dose, the choice of method is primarily one of individual preference.

Ratios

Using the equianalgesic chart in Table 9-1 as an example, note that the chart provides a list of analgesics at doses, both oral and parenteral, that are approximately equal to each other in the ability to provide pain relief. In other words, all the doses are theoretically interchangeable. All the opioid doses listed in the equianalgesic chart are appropriate starting doses given every 4 hours for adults with severe pain.

Example: Oral Morphine to IV Morphine

- Look at Table 9-1 and find the oral dose listed for morphine (30 mg) and the parenteral dose (10 mg).
- This gives a 30:10 or a 3:1 ratio for oral to parenteral morphine.
- This means that it takes approximately 3 times more morphine orally than parenterally (e.g., IV) to produce the same analgesic effect.
- One can simply divide any oral morphine dose by 3 to determine the approximate equianalgesic parenteral morphine dose.
- For safety reasons, this dose is often halved for initial dosing, because it may be difficult to predict side effects. The dose is increased if the patient tolerated the initial dose and needs additional pain relief.

Table 9-1

Equianalgesic Table Adapted from Goodman and Gilman, 9 th Edition		
Drug	Parenteral (mg)	Oral (mg)
Morphine	10	30 – 60**
Hydromorphone	1.3	7.5
Oxymorphone	1	5 (rectal)
Oxycodone	-	5-10*
Codeine	130	200
Hydrocodone	-	5-10*
Propoxyphene	-	65*
Meperidine	75	300
Levorphanol	2	4
Methadone	10	20
Fentanyl	0.1 µg	-
Nalbuphine	10	-
Butorphanol	2	-

*The dose of propoxyphene is not necessarily equivalent to 10 mg of subcutaneous morphine.

Example: Conversion from IV morphine to KADIAN®

- When converting IV morphine to oral morphine, use the same equianalgesic dose described above. In this instance, the ratio is 1:3.
- Simply multiply any IV morphine dose by 3 to determine the approximate equianalgesic oral morphine dose.
- If you want to take 20 mg IV total daily dose of morphine and convert it to KADIAN®, you would multiply 20 mg IV morphine by 3 to get 60 mg oral KADIAN® (60 mg once a day OR 30 mg twice a day).
- For safety reasons, KADIAN® may be started at a lower dose.

Proportions

Another method of calculating equianalgesic doses (EAD) is to set up simple math proportions using ratios. Use the following equation to calculate equianalgesic doses. Do a separate calculation for each old drug and route.

$$X = \text{Old dose} \times \frac{\text{New drug EAD}}{\text{Old drug EAD}}$$

Where X = Total daily dose of new drug

New drug EAD = Equianalgesic dose from chart of new drug and route

Old dose = Total daily dose of old drug

Old drug EAD = Equianalgesic dose from chart of old drug and route

Example: Conversion of KADIAN® to IV morphine

- Use the proportion equation to estimate the required parenteral morphine dose for a patient taking 60 mg of KADIAN®.
- In this example, the “new drug” will be IV morphine and the “old drug” is KADIAN®.
- Look at Table 9-2 to find equianalgesic doses for morphine IV (“New drug EAD”) and oral morphine (“Old dose”).

$$X = 60 \text{ mg} \times \frac{10 \text{ mg}}{30 \text{ mg}} = 20 \text{ mg}$$

- After you insert the numbers into the equation, you find that $X = 20 \text{ mg}$ IV morphine daily.
- Consider decreasing the total daily dose by 50% for safety (10 mg).
- The dose is then divided by the number of times a day the dose will be given. The dose interval is based on duration of action of the drug.
- IV morphine is given approximately every 4 hours, so 3 mg of IV morphine given every 4 hours would give the total of 10 mg (50% of the total calculated equivalent dose) given over 24 hours.
- This approach is likely to require a dosage increase in the first 24 hours for many patients (because it was started at 50% of the equivalent dose of the old drug), but is recommended because it is less likely to cause overdose or undesirable side effects than going directly to the calculated equivalent dose without titration.

Use of KADIAN® as the First Opioid Analgesic

There has been no evaluation of KADIAN® as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate the doses to achieve adequate analgesia when using extended-release morphine, it is ordinarily advisable to begin treatment with an immediate-release morphine formulation.

Opioid analgesic agents may not effectively relieve all types of pain. For example, neuropathic pain and headaches often require treatment with other types of medications containing analgesic properties. This does not mean that patients suffering from these types of pain should not be given an adequate trial of opioid analgesics. However, such patients may need to be promptly evaluated for other types of pain therapy.

Table 9-2

Equianalgesic Table Adapted from APS		
Drug	Parenteral (mg)	PO (mg)
Morphine	10	30

Hydromorphone	1.5	7.5
Oxymorphone	1	10 (rectal)
Oxycodone	-	20
Meperidine	75	300
Levorphanol	2(acute) 1 (chronic)	4(acute) 1 (chronic)
Methadone	10(acute) 2-4 (chronic)	20(acute) 2-4 (chronic)
Fentanyl	0.1	-

Individualization of Dosage

The use of opioid analgesics in the management of chronic malignant and chronic benign pain is described in materials published by the World Health Organization (WHO), the Agency for Health Care Research and Quality, and the American Pain Society, which are available from Actavis Pharmaceuticals LLC upon request. Treatment should be individualized by using appropriate pain management principals.

KADIAN® is a third-step drug that is most useful when the patient requires a constant level of opioid analgesia as a “foundation” or “baseline.” When a patient has reached the point where comfort cannot be provided with a combination of nonopioid medications (NSAIDs and acetaminophen) and intermittent use of moderate or strong opioids, the patient’s total opioid therapy should be converted into a 24-hour oral opioid equivalent. The addition of KADIAN® is done to provide a constant level of analgesia, and the level of analgesia can then be supplemented by the use of other medications (e.g., NSAIDs) as needed.

If breakthrough or incident pain occurs, the dose may be supplemented with a small dose (less than 20% of the total daily dose) of an immediate-release opioid analgesic. Patients who are excessively sedated after a once-a-day dose or who regularly experience inadequate analgesia before the next dose should be switched to Q 12 hr. dosing. If two or more breakthrough medications are needed, titration of the baseline or long-acting opioid medication should be done.

Pure mu-agonist opioids do not have a maximum dose.
Doses are titrated to pain relief, and so no ceiling can be

Pure mu-agonist opioids do not have a maximum dose; doses are titrated to pain relief.

given as to the recommended maximal dose. The total dose of KADIAN® should be advanced until the desired therapeutic endpoint is reached or clinically significant opioid-related adverse reactions occur.

Information for Patients

Patients receiving KADIAN® should be given the following instructions by the medical practitioner:

1. Patients should be advised that KADIAN® contains morphine and should be taken only as directed.
2. Patients should be advised that KADIAN® capsules should be swallowed whole (not chewed, crushed, or dissolved). Alternately, KADIAN® capsules may be opened and the entire contents sprinkled on a small amount of apple sauce immediately prior to ingestion. KADIAN® capsules or the contents of the capsules must not be chewed or crushed due to a risk of fatal overdose.
3. Patients should be advised that KADIAN® 100 mg and 200 mg Capsules are for use only in opioid-tolerant patients. Special care must be taken to avoid accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, as such unsupervised use may have severe, even fatal, consequences.
4. Patients should be advised that the dose of KADIAN® should not be adjusted without consulting the prescribing health care provider.
5. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
6. Patients should be advised that KADIAN® may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on KADIAN® or whose dose has been changed should refrain from dangerous activity until it is established that they are not adversely affected.
7. Patients should be advised that KADIAN® should not be taken with alcohol or other CNS depressants (sleeping medication, tranquilizers) except by the orders of the prescribing healthcare provider because dangerous additive effects may occur resulting in serious injury or death.

8. Women of childbearing potential who become or are planning to become pregnant, should consult their prescribing healthcare provider prior to initiating or continuing therapy with KADIAN®.
9. Patients should be advised that if they have been receiving treatment with KADIAN® for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the KADIAN® dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their prescribing healthcare provider should provide a dose schedule to accomplish a gradual discontinuation of the medication.
10. Patients should be advised that KADIAN® is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
11. Patients should be advised that severe constipation could occur as a result of taking KADIAN® and appropriate laxatives, stool softeners and other appropriate treatments should be initiated from the beginning of opioid therapy.
12. Patients should be instructed to keep KADIAN® in a secure place out of the reach of children. When KADIAN® is no longer needed, the unused capsules should be destroyed by flushing down the toilet.

FDA Safety Warnings for KADIAN®

The following are included in black box warnings from the FDA regarding KADIAN®:

- KADIAN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. KADIAN® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.
- KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.
- KADIAN® capsules are **NOT** for use as a **PRN** analgesic.
- KADIAN® 100-mg and 200-mg capsules **ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY**. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already

tolerant to high doses of opioids. KADIAN® capsules are to be swallowed whole or the contents of the capsules sprinkled on applesauce. The pellets in the capsules are not to be chewed, crushed, or dissolved due to the risk of rapid release and the absorption of a potentially fatal dose of morphine.

Additional warnings included in the prescribing information are as follows:

- KADIAN® may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

Summary

- KADIAN® is available in color-coded 10 mg (light blue) 20-mg (yellow), 30-mg (blue violet), 50-mg (blue), 60-mg (pink), 80-mg (light orange), 100-mg (green), and 200-mg (brown) capsules. KADIAN® capsules are administered orally once or twice daily (Q12 or Q24 hours). KADIAN® capsules should be swallowed whole (not chewed, crushed, or dissolved). Alternatively, KADIAN® capsules may be opened and the entire contents sprinkled on a small amount of applesauce immediately before ingestion, or the pellets can be mixed with a small amount of water and administered through a 16-French (or larger) gastrostomy tube. **The administration of KADIAN® pellets through a nasogastric tube should not be attempted.**
- KADIAN® may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.
- The pellets in KADIAN® should not be chewed, crushed, or dissolved because of a risk of overdose.
- Selection of the initial KADIAN® dosage should take into account the total daily dose, potency and characteristics of previously administered opioid analgesics, the reliability of the relative potency estimate used to calculate the total dose of morphine required, the patient's degree of opioid tolerance, the patient's general medical condition, other medications that the patient is concurrently taking, and the type and severity of the patient's pain.
- Patients already taking other oral morphine formulations can be converted to KADIAN® therapy by administering the patient's current total daily morphine dose of KADIAN® every 24 hours or one-half of the patient's current total daily morphine dose of KADIAN® every 12 hours, with subsequent dosage

adjustments as necessary.

- Patients already taking parenteral morphine or other parenteral or oral opioids should be converted with caution to KADIAN® because of individual patient variations and uncertainties regarding relative estimates of opioid potency and cross-tolerance. Only approximate guides as to the relative potencies of opioids are available. Researchers suggest that, for morphine, an oral dose 3 times greater than the parenterally administered dose is equipotent, but specific recommendations cannot be made for conversion from other parenteral or oral opioids to oral morphine. In these circumstances, the initial KADIAN® dosage regimen chosen should be conservative and 24-hour morphine requirements should, if anything, err on the side of underestimation.

Literature Cited

- Portenoy et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. Clin J Pain. 2007;23:287-299.
- Zech et al. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. Pain. 1995;63:65-76.

Self-Assessment Test

Circle the best response

- 1). Which of the following is not a KADIAN® capsule strength?
 - a. 20mg
 - b. 50mg
 - c. 80mg
 - d. 150mg
- 2). Which of the following is true regarding KADIAN® administration?
 - a. Administer orally every 12 or 24 hours.
 - b. Administer with meals.
 - c. Mix with applesauce and place in a 16-French or larger G-tube.
 - d. Sprinkle contents into applesauce up to 48 hours before ingestion.
- 3). Which of the following is true regarding the bioequivalence of KADIAN®?
 - a. KADIAN® is bioequivalent to other long-acting morphine products.
 - b. The area under the curve (AUC) of KADIAN® is similar to that of other controlled-release morphine products.
 - c. The C_{max} achieved with KADIAN® is greater than the C_{max} achieved by other controlled-release morphine products.
 - d. The slow release of morphine sulfate from KADIAN® reduces the area under the curve (AUC).
- 4). In patients who have not previously received opioids, the initial KADIAN® dose is:
 - a. 20 mg every 24 hours
 - b. 30 mg every 24 hours
 - c. 20 mg twice daily
 - d. 30 mg twice daily

- 5). When converting from parenteral morphine to oral morphine, the literature suggests giving an oral dose _____ times greater than the parenterally administered dose.
- 3 to 6
 - 5 to 10
 - 10 to 20
 - at least 100
- True or False**
- 6). When converting patients from other oral morphine preparations to KADIAN®, the initial once-daily KADIAN® dose would be equivalent to the patient's current total daily morphine dose every 24 hours.
- True
 - False
- 7). Excessive opioid side effects soon after conversion to KADIAN® should be treated by discontinuing KADIAN®.
- True
 - False
- 8). Any breakthrough or incident pain may be treated with a short-acting opioid analgesic.
- True
 - False
- 9). A patient's KADIAN® dose can be increased every 24 hours.
- True
 - False
- 10). KADIAN® impairs the central nervous system and motor skills less than do other opioids.
- True
 - False

Answers to Self-Assessment Test

1. d	6. a
2. a	7. b
3. b	8. a
4. a	9. b
5. a	10. b

CHAPTER TEN

Safety and Adverse Experiences

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Discuss the common adverse effects of KADIAN® and other opioids.
- Describe the potential serious adverse effects of KADIAN® and other opioids.
- Discuss the abstinence syndrome that can occur when chronic opioids are discontinued.
- Discuss the clinical manifestations of opioid overdose.
- Understand the use of opioids in pregnancy, labor and delivery, and breastfeeding.
- Identify the contraindications and precautions to the use of KADIAN®.
- Discuss potential drug interactions involving KADIAN®.

Terminology

Addison's disease:	A deficiency of the adrenal cortex and therefore the hormones produced in this area.
Amblyopia:	Weakness in vision in one eye that can cause it to relax and drift relative to the other (also called <i>lazy eye</i>).
Amenorrhea:	Lack of menstrual periods.
Ames test:	A test for potential carcinogenic properties of a drug. It uses the rate of genetic mutations caused in a strain of the bacterium <i>Salmonella</i> .
Amylase:	An enzyme that occurs in saliva and pancreatic juice and aids the digestion of starch. Amylase will also hydrolyze glycogen to yield glucose and other sugars.
Anaphylaxis:	A severe, life-threatening allergic reaction.
Antiemetic:	A drug that prevents nausea.
Arthralgia:	Joint aching.
Ataxia:	A lack of coordinated muscular movements that can result from neurologic disorders.
Atelectasis:	Collapse of the alveoli (tiny air sacs) in the lungs.
Axial skeletal fusion:	Calcification of the spinal column that leads to calcified connections between the bones, leading to a loss of motion.
Black box warnings:	Warnings required by the FDA for a product. They are called "Black Box" because they are required to be placed in a black box in a prominent position in the pharmaceutical information for a given drug ("package insert").
Biliary colic:	Abdominal pain that results from obstruction of the biliary tree (bile ducts or gallbladder).
Bradycardia:	Low heart rate.
Carcinogenic:	Any substances producing cancer.
Cimetidine:	A drug that reduces the production of stomach acid (also called Tagamet®).
Cordotomy:	A surgical procedure involving the division of the spinothalamic tract. The spinothalamic tract contains the nerve fibers responsible for transmitting the sensation of pain up the spinal cord.
Cytochrome (CYP) P450 isoenzymes:	Liver enzymes that metabolize drugs.
Decubitus ulcer:	An ulceration of the skin caused by pressure over a bony prominence.
Delirium tremens:	An alcohol withdrawal syndrome that results in confusion and hallucinations (DTs).
Detrusor muscle:	The muscle in the bladder that contracts to initiate urination.

Diaphoresis:	Sweating.
Edema:	Excessive accumulation of fluid in a tissue.
Embryocidal:	Causes death of an embryo in pregnant women.
Encephalopathy:	A disease or process causing abnormalities in the tissue of the brain.
Flaccidity:	A decrease in muscle tone.
Gastric stasis:	A relaxation of the stomach that causes it to not digest or propel its contents into the small intestine.
Hypercapnia:	The presence in the blood of an unusually high concentration of carbon dioxide.
Hyperpyrexia:	Increased body temperature (fever).
Hyperreflexia:	Excessively increased reflexes.
Hypotension:	Low blood pressure.
Hypothyroidism:	Low levels of thyroid hormones.
Hypoxia:	A deficiency of oxygen in a tissue.
In vitro:	Within a test tube.
In vivo:	Within the living body.
Inappropriate ADH secretion:	A syndrome in which antidiuretic hormone (ADH) is secreted abnormally.
Intraperitoneal:	Within the membrane of the abdominal cavity.
Kyphoscoliosis:	Abnormal curvature of the spine both forward and sideways.
Lethargy:	Extreme drowsiness from which it is difficult to rouse an individual.
Leukocytes:	White blood cells.
Malaise:	A generalized uncomfortable feeling that may be accompanied by physical discomfort.
Metastases:	The distant spread of a malignant tumor from its site of origin.
Miosis:	Contraction of the pupils.
Monoamine oxidase inhibitor:	A type of drug used to treat depression.
Mouse micronucleus test:	This is a commonly used test that determines whether a compound is able to cause chromosome aberrations in mice. It is used to predict genotoxicity (teratogenicity) of a new drug.
Mutagenic:	An agent that increases the rate of mutation.
Myalgia:	Pain in the muscles.
Myoclonic jerks:	Mild to moderate muscle contractions.
Myxedema:	A dry, firm, waxy swelling of the skin and subcutaneous tissues found in patients with underactive thyroid glands.
Noncardiogenic pulmonary edema:	A build-up of fluid in the lungs that is not caused by heart failure.

Nystagmus:	An abnormal sideways or up-and-down movement of the eyes that is associated with neurologic abnormalities or disease of the vestibular apparatus of the ear.
Pallor:	Paleness.
Pancuronium:	A drug used in anesthesia that paralyzes skeletal muscle.
Paralytic ileus:	Loss of motility of the small intestine.
Prostatic hypertrophy:	Enlargement of the prostate gland.
Q24h/Q12h:	Shorthand for every 24 hours and every 12 hours. Q is an abbreviation for <i>every</i> from the Latin <i>quaque</i> .
Rhinitis:	Inflammation of the mucous membranes of the nose.
Stomach atony disorder:	A condition caused by a loss of muscle tone in the stomach. It can lead to pain, nausea and vomiting, and distension.
Syncope:	Fainting.
T-cells:	White blood cells primarily responsible for cell-mediated immunity.
Teratogen:	An agent that induces the formation of abnormalities of the fetus.
Toxic psychosis:	Alterations of mental state caused by drug toxicity.
Urethral stricture:	Narrowing of the passage through which urine is voided.
Vasopressors:	Drugs that stimulate the contraction of blood vessels and therefore bring about an increase in blood pressure.
Vertigo:	Dizziness, specifically the type that causes a spinning sensation.

Introduction

The benefit of opioid therapy is generally very favorable when treatment is optimized. However, these medications do have potentially significant adverse effects. In addition, there are specific patient populations who should avoid or exercise caution when using KADIAN® and other opioids. Patients taking medications that cause sedation or central nervous system depression, phenothiazines, general anesthetics, or vasodilatory or other drugs that lower blood pressure should also be aware of the potential for serious adverse events when such medications are used concomitantly with opioids. This chapter will review the clinical presentations of these safety issues.

Opioid Adverse Reactions

The adverse effects of morphine, and therefore KADIAN®, are essentially the same as those observed with other opioid analgesics. Serious adverse reactions that may be associated with KADIAN® include:

- respiratory depression,
- respiratory arrest,
- circulatory depression,
- cardiac arrest,
- hypotension, and
- shock.

The less severe adverse effects include

- drowsiness,
- dizziness,
- constipation, and
- nausea and vomiting.

Adverse reactions are more likely to occur in opioid-naïve patients or with dosage increases in opioid-tolerant patients. In addition, the risk of an adverse effect increases as the dose of the opioid increases. Fortunately, most adverse effects are temporary. They will cease or decrease as opioid therapy is continued and some

degree of tolerance develops. Adverse effects should be expected and managed as a part of opioid analgesia.

Management of Constipation

Virtually all patients suffer from constipation while taking opioids chronically. Tolerance does not usually develop to this side effect. Thus, it requires an aggressive preventive approach, regular assessment, and aggressive management if symptoms are detected. Exercise, adequate fluid intake, eating bulk-containing foods, and taking natural colon stimulants such as prune juice will help to prevent constipation. The most common approach is to use a laxative regularly. Treatment continues as long as the patient takes opioids.

Management of Nausea and Vomiting

Nausea and vomiting are common after single doses of opioids or as an early undesirable effect of chronic opioid therapy. Vomiting accompanies nausea more often when constipation is not well controlled. Prophylactic treatment of nausea is not recommended because tolerance usually develops after several days. However, it may be necessary to use a scheduled antiemetic for the first week of therapy. A reduction in the dose by 10%-25% may also help reduce nausea. Persistent nausea and vomiting may be due to gastric stasis. Gastric stasis can be treated with metoclopramide, a drug that increases gut motility.

Management of Sedation

Most patients experience drowsiness at the onset of therapy or with a dose change. Tolerance to sedation usually develops over several days. If significantly sedated, patients should be discouraged from driving and operating mechanical equipment. Excessive or persistent sedation should be investigated. Factors that contribute to persistent sedation include the following: intolerance to the dose used, concurrent sedative medications, the presence of hepatic or renal insufficiency, hypoxia or hypercapnia due to exacerbated respiratory failure, disease severity, and the patient's general condition. If sedation continues, it can be managed with central nervous system stimulants such as methylphenidate, dexamphetamine, or modafinil.

Management of Myoclonus

Patients taking high doses of opioids often experience myoclonic jerks. If it disrupts sleep or causes an exacerbation of pain (e.g., bone metastases) changing to

another opioid may help. Mild myoclonus is common and resolves as tolerance develops. It can be treated with low doses of diazepam or clonazepam and other benzodiazepines.

Management of Skin Reactions

The itching, flushing, and rash that can occur because of the release of histamine will typically resolve in less than 2 weeks. Patient symptoms can be treated with antihistamines.

KADIAN® Clinical Safety

Clinical trials are often the best means of determining adverse event rates. KADIAN® has been evaluated in several clinical trials that have shown that its adverse events are similar to those of other opioids. These data were collected from several clinical studies of volunteers or patients who received KADIAN® in single doses or in repeated doses for periods of up to 14 days. Brief descriptions of the adverse event data from each of the repeated-dose studies (i.e., studies simulating typical clinical conditions) are presented below:

Broomhead A, et al. *J Pain Symptom Manage* 1997;14(2):63-73.

This parallel-group clinical study evaluated adverse event data collected over a 7-day treatment period for 61 patients receiving KADIAN® q24h, 52 patients receiving KADIAN® q12h, and 56 patients receiving MS Contin® q12h for treatment of moderate to severe cancer-related pain.

Central nervous system adverse events judged to be related to treatment had the highest frequency of adverse events: 11.5% in the KADIAN® q24h group, 13.5% in the KADIAN® q12h group, and 1.8% in the MS Contin® group. Despite the administration of high doses of morphine once daily in the morning in the KADIAN® q24h group, there was no significant difference among treatment groups for “nervous system” or other categories of adverse events. The incidence of emergent adverse events was acceptable for all three treatment groups given the patient population and the known side effects of morphine.

Floter T, et al. *Clin Drug Invest* 1997;14(3):183-191.

This parallel-group clinical study evaluated adverse event data collected over a 14-day treatment period for 104 patients receiving KADIAN® q12h and 74 patients receiving MS Contin® q12h for treatment of moderate to severe malignant or nonmalignant pain. Typical morphine-related adverse events were reported with a comparable incidence in both treatment groups: 24% for patients receiving KADIAN® q12h and 26% for patients receiving MS Contin® q12h.

Gourlay GK, et al. *Pain* 1997;69:295-302.

This two-period crossover study evaluated adverse events during 7-day treatment periods for 24 patients receiving KADIAN® q24h and MS Contin® q12h for treatment of severe cancer pain.

Both KADIAN® and MS Contin® q12h were associated with a low incidence of side effects. There were no significant differences between treatment groups in the incidence of nausea and vomiting, constipation, sedation, or appetite suppression. The only significant difference was observed on day 5 of treatment, when the incidence of confusion was higher in the KADIAN® q24h group. This difference, however, was considered a chance event because the assessments for confusion on the other assessment days were not significantly different.

Kerr RO, Tester WJ. *Clin Drug Invest* 2000;19(1):25-32.

None of the comparisons of tolerability between KADIAN® q24h and MS Contin® q12h had statistically significant differences. Most adverse events were those expected to occur with morphine, and the frequency and severity of morphine-related adverse events (nausea and vomiting, constipation, sedation, confusion, and appetite) for the KADIAN® treatment period were comparable with those for the MS Contin® treatment period. The percentage of patients who dropped out of the study because of adverse events (8% for KADIAN® and 5% for MS Contin®) and the percentage of patients experiencing serious adverse events (8% for KADIAN® and 9% for MS Contin®) were comparable during the KADIAN® and MS Contin® treatment periods.

Adverse Events – Single Dose and Repeated Dose

In controlled clinical trials in patients with cancer pain, the most frequently reported adverse events thought to be related to KADIAN® were drowsiness (9%), constipation (9%), nausea (7%), dizziness (6%), and anxiety (6%). Other less common side effects expected from morphine or seen in less than 3% of patients in the clinical trials are listed below.

- **Body as a Whole:** asthenia (muscular weakness), accidental injury, fever, pain, chest pain, headache, diaphoresis, chills, flu-like syndrome, back pain, malaise, withdrawal syndrome
- **Cardiovascular:** tachycardia, atrial fibrillation, hypotension, hypertension, pallor, facial flushing, palpitations, bradycardia, syncope
- **Central Nervous System:** confusion, dry mouth, anxiety, abnormal thinking, abnormal dreams, lethargy, depression, tremor, loss of concentration, insomnia, amnesia, paresthesia (abnormal sensation), agitation, vertigo, foot drop, ataxia (altered gait), hypesthesia (decreased sensation of touch), slurred speech, hallucinations, vasodilation, euphoria, apathy, seizure, myoclonus
- **Gastrointestinal:** vomiting, anorexia, dysphagia (difficulty swallowing), dyspepsia (heartburn), diarrhea, abdominal pain, stomach atony disorder, gastroesophageal reflux, delayed gastric emptying, biliary colic
- **Endocrine:** hyponatremia (low blood sodium) due to inappropriate ADH secretion, gynecomastia (breast development in males)
- **Hemic & Lymphatic:** anemia, leukopenia (low white blood count), thrombocytopenia (low platelet count)
- **Metabolic & Nutritional:** peripheral edema, hyponatremia (low sodium levels), edema
- **Musculoskeletal:** back pain, bone pain, arthralgia
- **Respiratory:** hiccup, rhinitis (runny nose), atelectasis, asthma, hypoxia, dyspnea (shortness of breath), respiratory insufficiency, voice alteration, depressed cough reflex, noncardiogenic pulmonary edema.
- **Skin and Appendages:** rash, decubitus ulcer, pruritus (itching), skin flush
- **Special Senses:** amblyopia, conjunctivitis, miosis, blurred vision, nystagmus, diplopia (double vision)
- **Urogenital:** urinary abnormality, amenorrhea, urinary retention, urinary hesitancy, reduced libido, reduced potency, prolonged labor

Most adverse events were mild or moderate in intensity. Overall, severe events were reported by 9% of patients receiving KADIAN®, 9% of patients receiving MS Contin®, and 15% of patients receiving immediate-release morphine. Sixteen patients discontinued clinical trials because of serious adverse events. In all except 5 of these patients (3 receiving KADIAN® and 2 receiving immediate-release morphine), the events were considered unrelated to the study medication. A total of 47 deaths occurred during the clinical trials of KADIAN®. All were attributable to disease progression, not to the medication.

Dependence and Withdrawal

Physical dependence develops to morphine with chronic use. Thus, the patient may experience the withdrawal/abstinence syndrome if morphine is abruptly discontinued. This is usually mild and is characterized by rhinitis, myalgia (muscle aches), abdominal cramping, and occasional diarrhea. Most observable symptoms disappear in 5-14 days without treatment. However, there may be a phase during chronic abstinence that lasts for 2-6 months characterized by insomnia, irritability, and muscle aches.

Overdose

Acute overdose with morphine is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, miosis, and sometimes pulmonary edema, bradycardia, hypotension, and death. Marked mydriasis (dilation) rather than miosis (constriction) may be seen due to severe hypoxia in overdose situations.

Primary attention is given to the reestablishment of an unobstructed airway and institution of assisted or controlled ventilation. Gastric contents may need to be emptied to remove unabsorbed drug when an extended-release formulation such as KADIAN® has been taken. Activated charcoal is given to help bind the drug and prevent it from being absorbed. The airway should be open before attempting treatment by gastric emptying or activated charcoal. Opioid antagonists may be given to block opioid receptors and prevent adverse effects of the drug. Supportive measures (including oxygen and vasopressors) are used in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

Respiratory Depression

Fear of respiratory depression prevents adequate opioid use. As long as there is pain, there is little likelihood that respiratory depression will occur. Close monitoring for respiratory depression is needed in opioid-naïve patients or when another pain intervention, such as an anesthetic block, takes away the pain stimulus.

If a patient arouses easily, he or she is unlikely to have respiratory depression. Treatment is considered when a patient has a persistent respiratory rate of <8 per minute (for 30 minutes or longer despite stimulation) or oxygen saturation < 90%. Patients may be encouraged to breathe by stimulating the painful area or by coaching the patient to breathe. Naloxone, an opioid antagonist, may be given to reverse the effects of the opioid and thus reverse the respiratory depression.

Antagonists

The pure opioid antagonists, naloxone, naltrexone, or nalmefene, are antidotes to the respiratory depression that results from opioid overdose. They work by blocking activity at the mu receptor. Use of an opioid antagonist is reserved for cases where such treatment is clearly needed. Opioid antagonists may have a shorter duration of action than some of the long-acting products such as KADIAN®. Thus, additional doses of the antagonist may be needed. KADIAN® will continue to release and add to the morphine load for up to 24 hours after administration, and the management of an overdose should be monitored accordingly.

Opioid-tolerant Individuals

Opioid antagonist agents should be administered cautiously to persons who are known or suspected to be physically dependent on KADIAN® or other opioids. Antagonist administration may cause a complete reversal of opioid effects and precipitate an acute withdrawal syndrome. Careful titration of opioid antagonists is necessary to treat serious respiratory depression in the opioid-dependent patient.

Contraindications for the Use of KADIAN®

KADIAN® is contraindicated (i.e., not to be used) in

- Patients with known hypersensitivity to morphine, morphine salts, or any of the capsule components of KADIAN® because of the risk of anaphylaxis.
- Patients with acute or severe bronchial asthma and those with respiratory depression. In these patients, KADIAN® would further compromise respiratory function through its depressant effects on respiration.
- Patients with obstruction of the gastrointestinal tract, especially a condition of the intestine known as paralytic ileus. The concern is that obstructions to the flow of material along the gastrointestinal tract could lead to retention of the drug in the stomach for an extended period, with subsequent release of a bolus morphine dose into the small intestine.

Precautions for the Use of KADIAN®

KADIAN® is intended for use in patients who require more than several days continuous treatment with a potent opioid analgesic. As with any potent opioid, it is critical to adjust the dosage regimen of KADIAN® according to the needs of each individual patient, bearing in mind any prior analgesic treatment.

Although it is not possible to mention every consideration that is important to the selection of the initial dose of KADIAN®, attention should be drawn to the following:

- The total daily dose, potency, kind, and characteristics (e.g., pure agonists or mixed agonists/antagonists) of previously administered opioid analgesics.
- The reliability of the equianalgesic dose equivalents used to calculate the total dose of morphine required.
- The patient's degree of opioid tolerance.
- The general condition and medical status of the patient.
- Other medications that the patient is concurrently taking.
- The type and severity of the patient's pain.

Cordotomy

Surgical treatment of pain may enhance the adverse effects of morphine on the respiratory system. Postoperative respiratory depression has occurred in a few isolated cases in patients treated with controlled-release morphine preparations before cordotomy. Patients who are scheduled for this or some other surgical procedure to interrupt pain transmission pathways should not receive KADIAN® within 24 hours of the procedure and pain should be managed with parenteral short-acting opioids. In addition, the post-procedure analgesics should be individualized through titration to avoid adverse effects.

Pancreatic/Biliary Tract disease

KADIAN® may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including pancreatitis. Opioids may cause increases in the serum amylase level.

Special Risk Groups

KADIAN® should be administered with caution, and in reduced dosages, to

- Patients who are elderly or debilitated and those with Addison's disease, myxedema, and hypothyroidism. These conditions increase the likelihood of morphine-induced respiratory depression.
- Patients with severe renal or hepatic impairment in whom the metabolism or excretion of morphine would be reduced, thus exacerbating any potential adverse effects.
- Patients with prostatic hypertrophy or urethral stricture. Morphine causes increased tone in the detrusor muscle of the urinary bladder, resulting in urinary urgency. At the same time, morphine also increases tone in the sphincter of the bladder, thus causing difficulty in urination. These effects exacerbate symptoms that are already present in prostatic hypertrophy and urethral stricture.
- Patients with central nervous system depression, toxic psychosis, acute alcoholism, or delirium tremens. These conditions are all exacerbated by morphine's effect on the central nervous system.
- Patients with severe kyphoscoliosis in which deformities of the spine reduce lung capacity.
- Patients undergoing biliary surgery and patients with acute pancreatitis secondary to biliary tract disease. Morphine potentially increases the tone of the sphincter of Oddi and may worsen biliary obstruction.

Driving and Operating Machinery

Morphine may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Patients must be cautioned accordingly. Patients should also be warned about the potential combined effects of morphine with other central nervous system depressants, including other opioids, phenothiazines, sedatives or hypnotics, and alcohol.

Carcinogenicity, Mutagenicity, and Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of morphine have not been conducted. There are no reports of carcinogenic effects in humans. *In vitro* (test tube) studies reported that morphine did not cause mutations in the Ames test with *Salmonella*. However, it induces chromosomal changes in human leukocytes and lethal mutations in *Drosophila*. *In vitro*, morphine was mutagenic in human T-cells, increasing the DNA fragmentation. *In vitro*, morphine was mutagenic in the mouse micronucleus test and induced chromosomal changes in spermatids and murine lymphocytes.

Chronic opioid abusers (e.g., heroin abusers) and their offspring display higher rates of chromosomal damage. However, the rates of chromosomal abnormalities were similar in unexposed individuals and in heroin users enrolled in long-term opioid-maintenance programs.

Pregnancy

Teratogenic Effects (Pregnancy Category C)

Morphine is classified by the FDA as a Category C drug in pregnancy (Table 10-1). Teratogenic effects of morphine have been reported in the animal literature. High parental doses during the second trimester were teratogenic in neurologic, soft, and skeletal tissue. The abnormalities included encephalopathy and axial skeletal fusions. These doses were often toxic to the mother and were 0.3- to 3-fold the maximum recommended human dose (MRHD) on a mg/m² basis. Morphine-induced maternal hypoxia and malnutrition may have contributed to the teratogenic

effects. Treatment of male rats with approximately 3-fold the MRHD for 10 days before mating decreased litter size and viability.

Nonteratogenic effects

Morphine given subcutaneously at toxic maternal doses to rats during the third trimester at approximately 0.15-fold the MRHD caused reversible reductions in brain and spinal cord volume, testes size and body weight in the offspring, and decreased fertility in female offspring. The offspring of rats and hamsters treated orally or intraperitoneally throughout pregnancy with 0.04- to 0.3-fold the MRHD of morphine show delayed growth, motor, and sexual maturation and decreased male fertility. Chronic morphine exposure of fetal animals' results in mild withdrawal, altered reflex and motor skill development, and alters responsiveness to morphine that persisted into adulthood.

There are no well-controlled studies of chronic in utero exposure to morphine sulfate in humans. However, uncontrolled retrospective studies of human neonates chronically exposed to other opioids in utero have shown reduced brain volume that normalizes over the first month of life. Infants born to opioid-abusing mothers are more often small for gestational age, have a decreased ventilatory response to CO₂ and an increased risk of sudden infant death syndrome. Morphine should only be used during pregnancy if the need for strong opioid analgesia justifies the potential risk to the fetus.

Table 10-1

FDA Pregnancy Risk Factor Classifications	
Category A	Controlled trials in women fail to demonstrate a risk to the fetus in the 1st trimester (and there is no evidence of risk in later trimesters), and the possibility of fetal harm appears remote.
Category B	Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled trials in pregnant women or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in their 1st trimester (and there is no evidence of risk in later trimesters).
Category C	Either studies in animals have demonstrated adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies

	in women and animals are not available. Drugs should be given only if the potential benefit justifies the risk to the fetus.
Category D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk, for example, if the drug is needed in a life-threatening situation or for a serious disease for which safe drugs cannot be used or are ineffective.
Category X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both and the risk of use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Labor and Delivery

KADIAN® is not recommended for use in women during and immediately prior to labor where short-acting and analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation that tends to shorten labor.

Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, such as naloxone or nalmefene, should be available for reversal of opioid-induced respiratory depression in the neonate.

Neonatal Withdrawal Syndrome

If a mother uses opioids during pregnancy, the fetus is also exposed. After birth, the newborn may experience neonatal withdrawal syndrome (NWS). Symptoms of NWS include irritability, hyperactivity, abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, weight loss, and failure to gain weight. The onset, duration and severity of the disorder differ based on such factors as the drug used, time and amount of mother's last dose, and rate of elimination of the drug from the newborn. Approaches to the treatment of this syndrome have included supportive care and, when indicated, drugs such as paregoric or phenobarbital.

Nursing Mothers

Low levels of morphine sulfate have been detected in human milk. Withdrawal symptoms can occur in breastfeeding infants when the mother discontinues morphine sulfate. Because of the potential for adverse reactions to nursing infants from KADIAN®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

There are studies from literature reporting the safe and effective use of both immediate- and extended-release oral morphine preparations for analgesia in children when dosed on a per kilogram basis. However, the safety of KADIAN®, both the entire capsule and the pellets sprinkled on applesauce, has not been directly investigated in patients below the age of 18 years. Moreover, administration of pellets by means of gastrostomy tube (G-tube) has not been investigated in pediatric patients. The range of doses available is not suitable for the treatment of very small children or those who are not old enough to take capsules safely. The applesauce sprinkling method is not an appropriate alternative for these patients.

Drug Interactions

Increasingly, it is recognized that clinically significant drug interactions can occur with opioids that result in additive side effects, or an increase or decrease in intended therapeutic effects of one or both medications. Drug-drug interactions are generally divided into two broad categories: pharmacodynamic and pharmacokinetic.

Pharmacodynamic interactions occur when there is an alteration in the pharmacologic activity of a drug resulting in antagonist, additive, or synergistic effects. These interactions generally do not involve changes in the actual plasma or tissue concentration of either drug involved. These interactions are common with opioid analgesics.

Pharmacokinetic interactions are those drug interactions that alter either the absorption, distribution, metabolism, or elimination of one or more administered drugs. Changes in these parameters are often the result of one or more cytochrome (CYP) P450 isoenzymes involved in oxidative metabolism.

Pharmacodynamic Interactions

Medications that can interact with opioid analgesics include agents with similar pharmacologic effects. Agents such as ethanol and benzodiazepines that cause central nervous system and respiratory depression should be used cautiously in the patient receiving opioids. Another common type of opioid pharmacodynamic interaction is the excitatory response or serotonin syndrome that may occur when opioids are used in combination with monamine oxidase inhibitors. Mental status change, hyperpyrexia, hyperreflexia, myoclonus, ataxia, diaphoresis, diarrhea, coma, and death characterize serotonin syndrome.

Pharmacokinetic Interactions

Absorption Interactions

Many types of absorption interactions result in changes in the amount of the drug absorbed or the rate at which a drug is absorbed. A decrease in the rate of absorption may result in failure of a drug to reach a therapeutic concentration even if the total amount of drug absorbed is unchanged. Any drug that slows gastric motility, such as anticholinergics or opiates, can slow the absorption rate. In other words, opioids can slow the absorption rate of other opioids.

Changes in the amount of drug absorbed may also be due to changes in gastrointestinal pH. Many medications require a specific gastrointestinal pH to be absorbed. Antacids, H₂-receptor antagonists, and proton pump inhibitors all increase the pH of the stomach. If a drug that requires an acidic pH is given with one of these medications, its absorption will be reduced.

Distribution Interactions

Protein-binding displacement interactions are common distribution interactions. Once absorbed, drugs are distributed by the blood as both free drug and protein-bound drug. Only the free or unbound fraction of the drug is active.

Any changes in the percentage bound can lead to a change in a drug's availability to receptor sites and its metabolism and excretion. When two or more highly protein-bound drugs are administered together, the two drugs may compete for the same binding site. This is competitive binding. As a result, one may increase the free fraction of the other, causing more active drug. Drug interactions of this class are complex but probably overstated. Drugs most likely to result in clinically important

interactions are greater than 90% protein-bound.

Metabolism Interactions

Metabolism is the process of breaking down drugs to metabolites both active and inactive so that they can be eliminated. Hepatic cells metabolize many drugs by an enzyme system called the cytochrome P450 system (CYP). Certain drugs are known to induce this enzyme system, which causes a drug to be cleared from the body more quickly. Other drugs may interact as enzyme inhibitors, increasing the length of time a drug remains in the body. The CYP system is broken down into individual enzymes called isoenzymes. Examples of isoenzymes include 3A4, 2C19, and 2D6. The 3A4 isoenzyme is responsible for most drug metabolism. However, CYP plays a potentially significant clinical role in opioid analgesic use.

For example, oxycodone is a substrate of CYP 2D6, meaning it requires this enzyme to be broken down and activated. Paroxetine, an antidepressant commonly used in pain management, is a potent inhibitor of 2D6. Thus, paroxetine can potentially inhibit CYP 2D6 and prevent the breakdown of oxycodone to its active metabolite. As a result, analgesic efficacy may be lost. Hydrocodone, codeine, oxycodone, and tramadol all require CYP 2D6 for activation. Table 10-2 lists examples of drugs that utilize the CYP 2D6 isoenzyme. Many cytochrome P450 interactions are theoretical and the clinical significance of such potential interactions is unknown.

Table 10-2

CYP 2D6 Enzyme Activity		
Substrates	Inhibitors	Inducers
Oxycodone	Celecoxib	Carbamezapine
Tramadol	Cimetidine	Ethanol
Hydrocodone	Citalopram	Phenobarbital
Codeine	Sertraline	Phenytoin
Meperidine	Paroxetine	Rifampin
Propoxyphene	Fluoxetine	
Methadone	Propoxyphene	
	Methadone	

KADIAN® Drug Interactions

Screening for drug interactions plays an important role in maximizing a patient's pain regimen while maintaining a level of safety. KADIAN® has few documented drug interactions. It is not highly protein bound. It is not metabolized by the cytochrome P450 enzyme system in the liver. Thus, interactions due to inhibition or induction of the enzymes do not occur. Below is a list of identified drugs that may have clinically significant interactions when given with KADIAN®.

Pharmacodynamic Interactions

Central Nervous System Depressants

KADIAN® should be used with great caution and in reduced dosages in patients receiving other medications which have depressant effects on the central nervous system. In such circumstances, there is increased risk of respiratory depression, hypotension, profound sedation, and coma. Examples of drugs that depress the central nervous system are sedatives, hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Consider a reduction in the dose by at least 50% of one or both medications.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (used as antidepressants) intensify the effects of morphine and other opioid drugs. The patient may become anxious and confused, and may experience significant depression of respiration with resultant coma. Monoamine oxidase inhibitors (MAOIs) are slowly eliminated from the body, which means any unwanted drug effects will persist. For these reasons KADIAN® should not be given to patients receiving MAOIs, or those treated with these drugs within the previous 14 days. Fortunately, MAOIs are rarely used today.

Diuretics

Morphine reduces the efficacy of diuretic drugs (which increase urine output) by stimulating the release of antidiuretic hormone. In patients receiving KADIAN® and diuretics, either an increase in diuretic dosage or an alternative therapy should be considered.

Mixed Agonist/Antagonist Opioid Analgesics

In theory, mixed agonist/antagonist opioid analgesics (such as pentazocine) should not be administered to patients treated with KADIAN® (or other pure opioid agonists), because these may reduce the analgesic effects of the pure opioid agonist or precipitate withdrawal symptoms.

Muscle Relaxants

KADIAN® may enhance the neuromuscular blocking effects of skeletal muscle relaxants, e.g., pancuronium, and thus produce an increase in respiratory depression. Downward adjustment of the dosage of skeletal muscle relaxant is advisable in such patients.

Pharmacokinetic Interactions

Gastrointestinal Agents

Absorption is not influenced by changes in stomach pH because absorption occurs in the intestines. H₂-receptor antagonists, proton pump inhibitors, and antacids lower the pH of the gut and theoretically could interfere with the release of morphine from KADIAN®, because this is a pH-dependent release. Clinical experience to date with KADIAN® provides no indication that concomitant administration of gastrointestinal agents affects the magnitude or duration of analgesia provided by KADIAN®. This may reflect the limited ability of such agents to raise the pH to a level needed for significant morphine release from the pellets as well as the limited amount of time the pellets typically spend in the stomach. No specific clinical trials evaluating the efficacy of KADIAN® in patients concurrently receiving antacids or gastric acid secretion inhibitors have been conducted.

Cimetidine

There has been one report of confusion and severe respiratory depression when a patient undergoing hemodialysis was administered morphine and cimetidine (an H₂-receptor antagonist drug used to treat stomach ulcers). Caution is required when KADIAN® and cimetidine are co-administered in patients receiving hemodialysis.

FDA Safety Warnings for KADIAN®

The following are included in the black box warnings from the FDA regarding KADIAN®:

- KADIAN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. KADIAN® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.
- KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.
- KADIAN® capsules are NOT for use as a PRN analgesic.
- KADIAN® 100-mg and 200-mg capsules ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids. KADIAN® capsules are to be swallowed whole or the contents of the capsules sprinkled on applesauce. The pellets in the capsules are not to be chewed, crushed, or dissolved due to the risk of rapid release and the absorption of a potentially fatal dose of morphine.

Summary

- As with any potent opioid, the dosage regimen of KADIAN® must be adjusted according to the needs of each individual patient, bearing in mind the factors outlined that should be considered when determining dosage. Some groups are also at special risk of the adverse effects of morphine, such as the elderly or debilitated and patients with Addison's disease, myxedema, hypothyroidism, renal or hepatic impairment, prostatic hypertrophy, or urethral stricture.
- KADIAN® should be administered with caution to patients with central nervous system depression, toxic psychosis, acute alcoholism, and those with biliary disease. Patients should be warned that morphine may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery, and of the potential combined effects of morphine with other central nervous system depressants, including other

opioids, phenothiazines, sedatives or hypnotics, and alcohol.

- Pregnant patients should be given KADIAN® only when the benefits clearly outweigh the potential risks to the fetus. KADIAN® is not recommended for use in women during and immediately before labor, and women should not breastfeed their infants when taking KADIAN®.
- Because of the risk of interactions, KADIAN® should not be administered to patients receiving monoamine oxidase inhibitors or mixed opioid antagonists/agonists and should be administered with caution in patients taking other central nervous system depressants or diuretics.

Self-Assessment Test

Circle the best response

- | | |
|--|--|
| <p>1) The most troublesome adverse effect of chronic therapy with KADIAN® and other opioid analgesics is _____.</p> <ol style="list-style-type: none"> Sedation Respiratory depression Constipation Nausea <p>2) Which of the following is true regarding nausea and vomiting associated with morphine therapy?</p> <ol style="list-style-type: none"> Nausea and vomiting is most common at onset of therapy or with dosage changes. Occurrence of nausea and vomiting requires discontinuation of the medication. Vomiting often accompanies nausea even when constipation is well controlled. Prophylactic treatment of nausea is recommended. <p>3) Which of the following is true regarding the concomitant use of gastrointestinal agents that decrease the acidity of the stomach with KADIAN®?</p> <ol style="list-style-type: none"> KADIAN® absorption is influenced by changes in stomach pH. Concomitant administration of gastrointestinal agents affects the magnitude and duration of analgesia provided by KADIAN®. Clinical trials evaluating the efficacy of KADIAN® in patients concurrently receiving antacids or gastric acid secretion inhibitors have been conducted. Drugs that lower the pH of the gut could theoretically interfere with the release of morphine from KADIAN®. <p>4) Which of the following patients is not at increased risk of respiratory depression with KADIAN®?</p> <ol style="list-style-type: none"> Elderly patients Severe asthmatics Hypothyroid patients Patients with prostatic hypertrophy | <p>5) KADIAN® may cause severe hypotension in patients whose ability to maintain blood pressure is already compromised by :</p> <ol style="list-style-type: none"> Increasing blood volume Vasodilation Hypertension Constricting blood vessels <p>6) Acute overdosage with morphine results in:</p> <ol style="list-style-type: none"> Agitation Somnolence Dilated pupils Increased respiratory rate <p>7) Opioid agonist-antagonists should not be administered with morphine because</p> <ol style="list-style-type: none"> Additional opioid analgesics should not be needed. Opioid agonist-antagonists block the mu receptor potentially causing withdrawal. Respiratory depression will occur. Analgesic tolerance will develop. <p>8) KADIAN® should be administered with caution to patients with _____.</p> <ol style="list-style-type: none"> Central nervous system depression Depression Diabetes Hypertension <p>9) KADIAN® classification as a category C in pregnancy means</p> <ol style="list-style-type: none"> It should never be administered in pregnancy. Morphine has inconclusive data defining the risk in pregnancy. There are no data showing morphine has teratogenic effects on the fetus. Morphine should be given only if the potential benefit justifies the risk to the fetus. <p>10) Signs of neonatal withdrawal syndrome include</p> <ol style="list-style-type: none"> Abnormal sleep pattern Excessive weight gain Dilated pupils Constipation |
|--|--|

***Self-Assessment Test
continued******True or False***

- 11) Qualitatively, the adverse effects of KADIAN® are essentially the same as those of other opioid analgesics including morphine sulfate solution.

True
False

- 12) Patients should be administered prophylactic therapy for constipation at the outset of KADIAN® treatment.

True
False

- 13) KADIAN® is recommended for administration to women during and immediately before labor.

True
False

- 14) The most common serious adverse effects of morphine are respiratory depression and apnea.

True
False

- 15) KADIAN® has many drug interactions due to its cytochrome P450 metabolism.

True
False

- 16) Patients who require a potent opioid analgesic for more than a few days are not suitable candidates for KADIAN®

True
False

- 17) KADIAN® should not be given to patients with acute or severe biliary obstruction.

True
False

Answers to Self-Assessment Test

1. c	10. a
2. a	11. a
3. d	12. a
4. d	13. b
5. b	14. a
6. b	15. b
7. b	16. b
8. a	17. a
9. d	

**SECTION
THREE**

Product Comparison

- Chapter 11: Opioid Product Comparison
- Chapter 12: Clinical Research Papers
- Glossary

CHAPTER ELEVEN

Opium Product Comparison

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- List each of the other opium products and their role in chronic pain management.
- Describe the differential features of each of the other opium products.
- List the modified-release formulations of the other opium products and their active ingredients and formulations.
- Discuss the advantages and disadvantages of each of the other modified-release opium products currently on the market.
- State the case for using KADIAN® in preference to the other opium products for the treatment of chronic pain.

Introduction

Optimizing analgesic treatment with opioids relies on individualization of therapy and an understanding of comparative pharmacology. Several factors can determine the opioid of choice, including mechanism and site of action, pharmacokinetics (including those of different drug formulations), metabolism, and adjuvant drug administration.

Conventional, immediate-release formulations of opioids have been available for a long time. The challenge in improving chronic pain management has not been in the development of new drugs with new actions or better potency, but rather in the way in which the drug is delivered. This chapter will review the commonly prescribed agents used to manage chronic pain and compare these medications with KADIAN®.

Opioid receptors

Opioid receptors in the central nervous system are the point at which opioid drugs (and endogenous opioids) exert their pharmacologic action. Different types of opioid drugs act as agonists or antagonists at these different receptors. Because activation or blockage of different receptors results in different clinical responses, understanding a drug's actions at these receptors makes it easier to understand the benefits and adverse effects of different opioid drugs.

There are three main classes of opioid receptors, mu, kappa, and delta, and each class has subtypes (e.g. mu1 and mu2). Most opioids primarily activate mu receptors, but some opioids interact with kappa receptors as well. When activated by an agonist, the mu receptor mediates analgesia, decreases respiratory function, decreases transit time in the digestive tract, and causes sedation. Some subtypes of kappa receptors also mediate analgesia and decrease digestive tract transit time, but they also can trigger hallucinations and increase urination (agonist actions). Receptor antagonists block these actions; therefore, a mixed agonist/antagonist agent may block some of these effects (e.g., analgesia) while activating others. Although the mixed agonist/antagonist drugs have clinical usefulness in other settings, they are not generally used for chronic pain management, in part because of their ceiling effect for analgesia and antagonist activity at the mu receptor.

KADIAN® Review

(Actavis Pharmaceuticals, LLC)

Indication

KADIAN® is recommended for the management of moderate to severe pain when treatment with an opioid analgesic is indicated for more than a few days.

Available Strengths

Color-coded gelatin capsules in 8 strengths: 10 mg (light blue), 20 mg (yellow), 30 mg (blue violet), 50 mg (blue), 60 mg (pink), 80 mg (light orange), 100 mg (green), and 200 mg (brown).

Delivery System

KADIAN® capsules contain polymer-coated, sustained-release pellets of morphine sulfate in a capsule. The gelatin capsule dissolves quickly in the stomach, freeing the polymer-coated pellets. As the pellets pass into the less acidic small intestine, morphine release is greatly accelerated. The pellets develop minute holes through which the morphine diffuses. The pellets are formulated so that morphine is released over several hours, resulting in plasma morphine concentrations that are maintained for up to a 24-hour period.

Dosage and Administration

KADIAN® is administered once or twice daily (Q12 or 24 hrs). Patients who do not have a proven tolerance to opioids should be started on only the 20-mg strength. Dosage increases should generally be separated by 48 hours. As with all long-acting opioids, breakthrough pain may require supplementation with short-acting (immediate-release) morphine.

In general, capsules (and pellets) should be swallowed whole and should not be chewed, crushed, or dissolved. As alternatives to ingesting whole capsules, capsules may be opened and the pellets ingested with a small amount of applesauce or administered through a 16-French or larger gastrostomy tube (G-tube) with a small amount of water. The administration of KADIAN® pellets through a nasogastric tube (NG) should not be attempted.

The safety and effectiveness of KADIAN® in pediatric patients below the age of 18 has not been established. The range of dose may not be appropriate for this patient population. Sprinkle administration is not a suitable alternative for these patients.

Pharmacokinetics

After the administration of KADIAN®, approximately 50% of the morphine absorbed reaches the systemic circulation within 8 hours. This absorption is minimally affected by the presence of food. The product continues to release medication up to 24 hours.

KADIAN® is distributed to the skeletal muscle, kidneys, liver, gastrointestinal tract, and brain. It is also secreted into breast milk and crosses the placenta. Morphine does not accumulate in tissues when given in normal doses.

Morphine is 30% to 35% bound to plasma protein, which makes it a low-protein-binding drug.

Morphine is conjugated into M3G and M6G glucuronides in the liver. Both compounds are water-soluble glucuronides that require renal elimination for clearance. M3G appears to be antinociceptive and has been associated with hyperalgesia and neurotoxicities. M6G possess significant analgesic activity.

The pharmacokinetics of morphine are altered in hepatic and renal disease. Adjustment of morphine doses may occasionally be necessary in hepatically or renally impaired patients to prevent drug accumulation including accumulation of metabolites.

Side Effect Profile

- Constipation, drowsiness, nausea and vomiting, and dizziness or light-headedness are the most common adverse effects in normal doses.
- Other adverse effects include cardiovascular alterations (e.g., flushing of the face, bradycardia, tachycardia, palpitations), central nervous system effects (e.g., confusion, hallucinations, restlessness, vertigo), gastrointestinal tract effects (e.g., anorexia, biliary colic), genitourinary tract effects (e.g., urinary retention, hesitancy, inappropriate antidiuretic hormone secretion), visual disturbances (e.g., blurred vision, diplopia, nystagmus, miosis), hypothermia, dermatological effects (e.g., urticaria and pruritus), allergic and anaphylactic reactions, and the withdrawal (abstinence) syndrome.

- Major hazards in large doses are respiratory depression, circulatory depression, respiratory arrest, and cardiac arrest or shock.

Contraindications/Precautions

Contraindications are similar to immediate-release morphine, with the addition of gastrointestinal obstruction and particularly paralytic ileus. Caution should be used when administering KADIAN® within 24 hours of cordotomy or similar surgery.

Black box warning:

KADIAN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. KADIAN® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

KADIAN® Capsules are NOT for use as a prn analgesic.

KADIAN® 100 mg and 200 mg Capsules are for use in opioid-tolerant patients only. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids. KADIAN® capsules are to be swallowed whole or the contents of the capsules sprinkled on apple sauce. The pellets in the capsules are not to be chewed, crushed, or dissolved due to the risk of rapid release and absorption of a potentially fatal dose of morphine.

Alcohol use warning: KADIAN® may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

Advantages

- KADIAN® contains morphine, which is the gold standard analgesic for moderate

to severe chronic pain.

- Oral delivery of medication is the preferred route in chronic pain management. KADIAN® is available in 8 strengths of oral morphine that allow titration in 10-mg increments.
- KADIAN® has flexibility in administration by oral, sprinkle, and G-tube routes.
- KADIAN® is not metabolized by the cytochrome P450 system. Therefore, there is no need to monitor drug interactions through this system.
- There is little potential for drug interactions involving protein binding due to low binding of morphine (30% to 35% protein bound).
- The plasma morphine profile following KADIAN® administration is characteristic of an extended-release formulation. The maximum concentration C_{max} is reduced and the time to maximum concentration (t_{max}) is delayed with respect to immediate-release morphine.
- The pharmacokinetics of morphine are linear over the dosing range of 30 to 100 mg. Thus, increases in doses provide predictable increases in plasma concentrations.
- KADIAN® administered once daily may improve compliance compared with that for other controlled-release formulations administered more often.
- The KADIAN® adverse event profile is similar to that for other opioid analgesics.
- The q24h dosing interval allows KADIAN® to be synchronized with the patient's sleep cycle to improve sleep and minimize side effects. Peak levels, which are more often associated with side effects, are delayed 8 hours from administration, and this peak effect may occur during the night if dosing is timed appropriately.

Long-Acting Opioid Product Comparison: Duragesic®, Methadone, OxyContin®

Disadvantages

- Morphine doses may require adjustment in renal and hepatic disease to prevent drug accumulation.
- Morphine is associated with slightly more gastrointestinal side effects than are other opioids.

Duragesic® (transdermal fentanyl patch)

Fentanyl is a synthetic opioid that was first introduced as an alternative to morphine in 1960. For the next 30 years, it was available only in an injectable form and was used primarily as an anesthetic. It is not effective orally because the liver breaks it down quickly. In 1990, it was introduced in a skin patch (Duragesic®) that delivers a steady level of medication for 72 hours (Table 11-1).

Indication

The transdermal product is used in the management of chronic pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, nonsteroidal analgesics (NSAIDs), or PRN dosing with short-acting opioids and that requires continuous opioid administration for an extended period of time. The fentanyl patch should be used only in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose of at least the equivalent of fentanyl 25 mcg/h.

Table 11-1

Formulation	Products (Manufacturers)	Dosing Interval
Transdermal patch	Duragesic® 12 mcg/h, 25 mcg/h, 50 mcg/h, 75 mcg/h, 100 mcg/h Fentanyl Transdermal Patch (generic) 12 mcg/h, 25 mcg/h, 50 mcg/h, 75 mcg/h, 100 mcg/h	q48 to 72 h

Contraindications/Black box warnings:

Duragesic® contains a high concentration of a potent schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (Duragesic®) may be a particular target for abuse and diversion.

Duragesic® is indicated for management of persistent, moderate to severe chronic pain that requires continuous, around-the-clock opioid administration for an extended period of time, and cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.

Duragesic® should only be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to Duragesic® 25 mcg/h. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, Duragesic® (fentanyl transdermal system) is contraindicated:

- in patients who are not opioid-tolerant
- in the management of acute pain or in patients who require opioid analgesia for a short period of time
- in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)
- in the management of mild pain
- in the management of intermittent pain [e.g., use on an as needed basis (prn)]

Since the peak fentanyl levels occur between 24 and 72 hours of treatment, prescribers should be aware that serious or life threatening hypoventilation may occur, even in opioid tolerant patients, during the initial application period.

The concomitant use of Duragesic® with potent cytochrome p450 3a4 inhibitors (ritonavir, Ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving Duragesic® and potent cyp3a4 inhibitors should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted.

The safety of Duragesic® has not been established in children under 2 years of age. Duragesic® should be administered to children only if they are opioid-tolerant and 2 years of age or older.

Duragesic® is only for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the Duragesic® dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean elimination half-life of 17 hours of Duragesic®, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

Duragesic® can be abused in a manner similar to other opioid agonists, legal or illicit. This risk should be considered when administering, prescribing, or dispensing Duragesic® in situations where the healthcare professional is concerned about increased risk of misuse, abuse or diversion.

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

Duragesic® patches are intended for transdermal use (on intact skin) only. Using damaged or cut Duragesic® patches can lead to the rapid release of the contents of the Duragesic® patch and absorption of a potentially fatal dose of fentanyl.

Interactions with alcohol: fentanyl may be expected to have additive CNS depressant effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Pharmacology

Fentanyl citrate is a synthetic mu agonist with pharmacologic effects similar to morphine and meperidine. Its chemical structure most closely resembles meperidine. Fentanyl is 50 to 100 times as potent as morphine on a weight basis; fentanyl 0.1mg is approximately equivalent in analgesic activity to morphine 10mg or meperidine 75mg.

Available data indicate that histamine release, which can cause hypotension, tachycardia, and erythema, rarely occurs with fentanyl, even with use of large doses (50 to 150 mcg/kg).

Delivery System

Duragesic® (fentanyl transdermal) is a skin patch that contains a reservoir of fentanyl and alcohol gelled with hydroxyethyl cellulose. The system delivers less than 0.2 milliliters of ethanol over the 72-hour period of use. Fentanyl is delivered to the skin forming a depot of drug in the upper layers, from which it enters the circulation. An ethylene-vinyl acetate copolymer membrane controls the rate of delivery of fentanyl to the skin surface. The delivery rate is directly proportional to the area of the membrane in contact with the skin, and using patches with different membrane surface areas achieves different infusion rates. Thus, each of the 5 available strengths has a different surface area (See Table 11-2).

The membrane of the patch is coated with a silicon-based bioadhesive that holds the patch in intimate contact with dry or hydrated skin for up to 3 days in temperatures ranging from 0° to 40°C. If properly applied, the patch will adhere while the patient bathes or showers.

Table 11-2

Duragesic® Patch Surface Area and Rate of Delivery		
Patch Size	Fentanyl Content	Rate of Delivery
5 cm ²	1.25 mg	12.5 mcg/h
10 cm ²	2.5 mg	25 mcg/h
20 cm ²	5.0 mg	50 mcg/h
30 cm ²	7.5 mg	75 mcg/h
40 cm ²	10 mg	100 mcg/h

An increasing body of evidence supports the fact that Duragesic® prescription abuse is less common than with some other opioids. The drug may be difficult to extract from the patch. Quantities that are extracted, however, are large enough to kill even opioid-tolerant abusers. The reservoir nature of the patch prevents the abuser from

accurately extracting a specific amount of drug (refer to Chapter 6).

Dosing and Administration

The transdermal patch has a broad equivalency range to oral morphine. See Table 11-3 for corresponding morphine doses. In controlled clinical trials in opioid-tolerant patients, 60mg/day oral morphine was considered to provide analgesia approximately equivalent to Duragesic® 25 mcg/h. Doses greater than 25 mcg/h should not be used for initiation of therapy in non-opioid-tolerant patients. When doses greater than 100 mcg/h are required, multiple patches are used. Due to the broad equivalency ranges, 50% of Duragesic® patients will require a dose increase shortly after the start of therapy.

Table 11-3

Duragesic® Equivalency to PO Morphine	
PO 24 hour Morphine (mg/day)	Duragesic® Dose (mcg/h)
60-134	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

Duragesic® requires patient education regarding proper patch application. The patch must be applied to an intact, nonirritated, clean, nonhairy site on the upper torso or upper arm. It must be held in place for a minimum of 30 seconds to ensure adhesion.

Patients and healthcare workers must be instructed on the disposal of the patch. Current instructions state that the patch must be disposed of properly by folding the patch in half (with the adhesive side adhering to itself inside the fold) and flushing it in the toilet.

Duragesic has been studied in doses of 25 mcg/h and higher in children aged 2 to 19 years who had been previously receiving daily opioid doses of at least 45 mg of oral morphine (or the equivalent). Initiation of therapy in patients aged 2 to 18 years who were on less than 60 mg/day of morphine has not been studied. Duragesic® has not been studied in children under the age of 2 years. Duragesic® should only be administered to children who are opioid tolerant and are 2 years old or older.

Pharmacokinetics

The uptake of fentanyl through the skin is relatively slow and constant, even when the location of the system is varied. The skin does not metabolize the drug, and 92% of the dose is delivered into the bloodstream as intact fentanyl. Body temperature can accelerate the absorption of fentanyl (increasing body temperature from 37° to 40°C has been shown to increase absorption by up to 33%).

Serum fentanyl concentrations are measurable within 2 hours after application of the first patch, and analgesic effects can be observed 8 to 16 hours after application. This delay is required to establish a reservoir of fentanyl in the stratum corneum of the skin. It can take 12 to 72 hours for serum fentanyl concentrations to level off. Steady state is not reached until after several sequential patch applications.

Fentanyl is highly soluble in lipids. It accumulates in skeletal muscle and fat and is slowly released into the blood. Plasma half-life is 3 to 4 hours after parenteral administration. However, after removal of the Duragesic® patch, systemic absorption of residual fentanyl in the skin continues. Serum drug levels fall slowly with a variable half-life of about 17 hours (range 13-22 hours). In other words, serum fentanyl levels will fall to 50% in approximately 17 hours.

Fentanyl is rapidly metabolized, primarily by dealkylation, to inactive metabolites in the liver. It is excreted mostly as metabolites in the urine. The presence of inactive metabolites makes it a preferred drug in patients with liver dysfunction.

Drug Interactions

Fentanyl is a CYP3A3/4 enzyme substrate. Medications that inhibit these enzymes (erythromycin, ketoconazole, itraconazole, and protease inhibitors) may increase serum concentrations of fentanyl. Drugs that increase metabolism through CYP3A3/4, (carbamazepine, phenobarbital, and rifampin) may decrease serum levels of fentanyl by increasing its metabolism. However, whether these interactions are clinically significant is unknown. (See Appendix 11-2 for further information.)

Side Effect Profile

- The side effect profile of fentanyl is similar to morphine, although fentanyl is less likely to cause nausea and vomiting when used in equivalent doses. Unfortunately, the conversion from oral morphine to Duragesic® is so broad that patients are often given aggressive doses of Duragesic® and nausea becomes a problem. As with all opioids, tolerance does develop to side effects (except constipation).
- At high doses, fentanyl can produce marked muscular rigidity. However, this side effect is typically associated with rapid IV infusion and not with Duragesic® patches.
- Fentanyl transdermal delivery eliminates first-pass metabolism in the liver.
- Because transdermal delivery eliminates absorption from the GI tract, constipation has been reported to be less frequent than that seen with other opioids.
- Skin rash around the patch is a common side effect. However, this can often be prevented by pretreating the skin with a steroid spray (e.g., the kind that is used in steroid inhalers for asthma). Clinically, the incidence of patch intolerance is believed to be greater than the 3% to 10% reported in the package insert.
- Adverse effects can persist for up to 36 hours after removal of the patch because of continued absorption of the drug in the skin.

Advantages

- Fentanyl is a potent opioid. It is less likely than morphine to cause nausea and vomiting when used in equivalent doses.
- Duragesic® is a good alternative for those who cannot take oral medications.
- In the current sustained-release market, fentanyl is the drug of choice in patients with liver dysfunction.

- The incidence of rash, itching, flushing, and hypotension is lower than for morphine because of minimal histamine release.
- The transdermal patch is believed to be less abusable than OxyContin® and MS Contin®.
- Available as a generic

Disadvantages

- No tablet or capsule formulation of fentanyl is available.
- Patients require education regarding patch application.
- Dose increase should only occur every 6 days.
- Equivalent dosing to morphine is difficult to determine.
- The analgesic effect cannot be evaluated during the first 24 hours because of the delay of onset of Duragesic® patch.
- Patches often do not last 72 hours, requiring more frequent change and increasing cost.
- Some patients, particularly the elderly, may have difficulty remembering what day to change their patch.
- Patients may have allergies to the patch adhesive.
- With the Duragesic® patch, patients must use short-acting analgesics for the first 24 hours as needed.
- Duragesic® cannot be used for acute pain because of the difficulty in titrating the dose.
- Large dose strength patches are quite wide (2-3 inches across).
- Doses greater than 100 mcg/h require multiple patch applications, which can be very expensive.
- Patients with adverse reactions to Duragesic® should be monitored for at least 12 hours after patch removal.
- Patients should be advised to avoid exposing the Duragesic® application site to direct external heat sources (e.g., heating pads, heat lamps, hot tubs, etc). There is a potential for temperature-dependent increases in fentanyl release from the patch. Theoretically, fever may also increase fentanyl release from the patch.
- There has been no systematic evaluation of Duragesic® as an initial opioid in the treatment of pain.

Advantages of KADIAN® Over Duragesic®

- No patient education regarding appropriate application of the product is required before administration of KADIAN®.
- KADIAN® is not metabolized by cytochrome P450 3A4 like Duragesic®, therefore avoiding drug interactions through this system. (See Appendix 11-2 for more information.) Drug interactions may lead to less efficacy or greater adverse events associated with drugs that use the P450 3A4 cytochrome system for metabolism.
- Duragesic® 25 mcg may be equivalent to 60 mg daily of oral morphine (12 mcg patch is now available). Morphine can be initiated at a much lower dose.
- The rate of drug delivery from KADIAN® is not increased by external heat sources.
- Steady state is achieved in 2 days with KADIAN® versus approximately 1 week with Duragesic®. Dose titration can be done much more rapidly with KADIAN®.
- Dose titration is easier with KADIAN®. KADIAN® is available in capsules containing 10, 20, 30, 50, 60, 80, 100, and 200 mg of morphine. The 10-mg capsule is the lowest available strength of extended-release morphine.
- At steady state, Duragesic® provides the same blood level at all times. KADIAN® can be administered so that peak blood levels occur at the most opportune time—either during sleep to minimize side effects, or at the time of day when the patient has the most severe pain.
- Oral administration is the preferred route for treatment of pain due to cost and convenience. Duragesic® is not available in an oral formulation and costs more than KADIAN®.

Methadone

Methadone was first synthesized in Germany at the end of World War II and was specifically designed for the treatment of severe chronic cancer pain. In the middle 1960s it became widely used to treat drug addicts because it can suppress drug-craving in this population with one daily dose. Because of this, it has developed a reputation as a medication that is linked to addiction. Actually, it is an excellent pain medication that probably has lower abuse potential than some other opioids (refer to Chapter 6).

Indication

Methadone is indicated for the management of severe pain. It is also used in detoxification and maintenance treatment of narcotic addiction. If used for detoxification and maintenance treatment of narcotic addiction, it must be part of an FDA-approved program.

Contraindications/Black box warnings:

Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists. It is critical to understand the pharmacokinetics of methadone when converting patients from other opioids.

Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration.

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

In addition, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if the potential analgesic or palliative care benefit of treatment with methadone is considered and outweighs the risks.

Table 11-4

Available Methadone Products		
Formulation	Products (Manufacturers)	Dosing Interval
Tablets	Dolophine® 1 mg, 5 mg, 40 mg Methodose® 5 mg, 10 mg, Methadose Dispersible Tablet 40 mg Diskets Orodispersable Tablet 40 mg	q3 to 8h
Oral solution	Methadose Concentratione Liquid 10 mg/mL Methadone Solution 10mg/5mL	q3 to 8h

Pharmacology

Methadone is a potent mu agonist with a unique chemical structure. It is considered by some to be the best strong alternative for morphine-intolerant patients. Because it has effects on other receptors (NMDA receptors) in addition to opioid receptors, methadone is sometimes effective for treating pain that does not respond to other opioid medications.

Methadone is a true long-acting opioid. It has a half-life of up to 55 hours in some patients. Other long-acting opioids are modified-release formulations for short half-life drugs.

In single doses, methadone is only marginally more potent than morphine: 10 mg IM or 20 mg PO is equivalent to morphine 10 mg IM or 60mg PO. In repeated doses, methadone is several times more potent than morphine; oral doses of 20-30 mg are equianalgesic to 60-90 mg or more of morphine PO. However, the equianalgesic conversions for methadone are considered less reliable than for most other opioids.

The peak respiratory depression effect of methadone occurs later and lasts longer than the peak analgesic effect. Thus, adequate analgesia could potentially be associated with a delayed respiratory depression effect, particularly in the early dosing period. This can contribute to iatrogenic (induced inadvertently by medical treatment) overdose.

NOTE: Conversion to methadone from other opioids is notoriously unpredictable. For this reason, the American Society of Addiction Medicine has recently recommended that methadone be started at no more than 25% of the expected conversion dose.

Dosing and Administration

Methadone is unique in that its dosing intervals do not correlate with its half-life. Drugs with long half-lives usually are dosed once daily. Methadone requires divided doses to maintain analgesic efficacy. The duration of action of methadone is approximately 4 to 6 hours following oral administration (i.e., similar to morphine). The duration of action may extend to 6 to 8 hours after repeated administration. Typical starting doses range from 5 to 30mg daily in divided doses. Onset of analgesia varies from 30 minutes to 4 hours with peak concentrations occurring at 2 to 4 hours. Methadone is occasionally used every 3 to 8 hours as a PRN medication.

Dose titration is more difficult with methadone than with morphine. The patient must be stable for 2 to 3 days before gradual increases in the dose are initiated. In some cases, the methadone dose may need to be decreased 3 to 5 days after initiation to prevent toxic effects due to drug accumulation in the tissues.

Pharmacokinetics

Methadone is readily absorbed from the gastrointestinal tract, reaching peak concentrations after about 4 hours. After therapeutic doses, about 90% of methadone is bound to plasma protein. It is widely distributed in tissues. Methadone is found in low concentrations in blood and brain, with higher concentrations in kidney, spleen, liver, and lung. It readily crosses the placenta; concentrations in amniotic fluid approach those of maternal plasma.

Methadone is extensively metabolized in the liver, mainly by *N*-demethylation. This appears to be mediated by several cytochrome P450 enzymes, which means there is a potential for drug interactions if the patient is taking other drugs that are metabolized by the P450 enzymes (*see* Appendix 11-2). The major metabolites are excreted in the bile and urine. Terminal half-life is extremely variable (15 to 55 hours); therefore, accumulation is possible and dosing intervals need to be carefully monitored.

Methadone appears to be firmly bound to protein in various tissues, including the brain. After repeated administrations, there is gradual accumulation in tissues. The

risk of accumulation is more likely in patients with impaired renal or hepatic function, because both organs are involved with the metabolism of methadone.

Like morphine, methadone displays wide variability between individuals in concentrations of drug achieved in the blood and rate of elimination of drug from the body after parenteral administration. Dosage schedules of methadone must therefore be individualized for each patient.

Drug Interactions

Methadone is a CYP1A2, 2D6, and 3A3/4 enzyme substrate and a CYP2D6 enzyme inhibitor. CYP3A3/4 and CYP2D6 enzyme inhibitors may increase serum methadone concentrations, potentially leading to toxicity, although no cases are reported in the literature. Enzyme inducers decrease serum methadone concentrations via enhanced hepatic metabolism. Inducers such as phenytoin, pentazocine, ritonavir, and rifampin may increase the metabolism of methadone, which could lead to inadequate pain control. See appendix 11-2 for more information.

Due to high protein binding of methadone, it is possible that methadone interacts with other highly protein-bound drugs such as digoxin and warfarin; however, no such interactions have been reported in the literature. Drugs that are highly protein-bound may be displaced from their binding sites by competition with other protein-bound drugs. This can lead to unpredictable levels of unbound drug (available drug).

Side Effect Profile

- The side effect profile of methadone is similar to that of morphine, but methadone has a greater respiratory depressant effect than morphine.
- Pulmonary edema after overdosage is a common cause of fatalities among addicts.
- Deaths from methadone overdose have been on the rise. A public health data base in Utah found that methadone use for pain treatment had increased 727% and was associated with a 1770% increase in methadone-related deaths. Several theories to the dramatic increase in death exist. (Sims 2007) One theory is that patients switched to methadone from other highly abused opioids misuse the product. The accumulation of the drug in the tissue makes it a very unpredictable product when not used appropriately.
- Recently, methadone has been associated with QT interval elongation and

torsades de pointes, an atypical rapid ventricular tachycardia, at an average dose of 400 mg per day.

- A black box warning from the FDA states that both cardiac and respiratory deaths have been reported during initiation and conversion of pain patients to methadone.

Advantages

- The extended duration of action is advantageous for patients with chronic benign pain except for the tendency of the drug to accumulate.
- Methadone is sometimes effective for treating pain that does not respond to other opioid medications as the result of activity at NMDA and other receptor sites.
- Tolerance may develop more slowly to methadone than to morphine in some patients.
- Methadone is less expensive than other long-acting opioids.
- Methadone is very effective in suppressing withdrawal symptoms in patients dependent on opioids.

Disadvantages

- The sedative properties of methadone are greater than those of morphine.
- Respiratory depression effects typically occur later and persist longer than the peak analgesic effects, particularly in the early dosing period.
- Repeated administration may lead to accumulation of the drug (with potential for significant toxicity) because of very long half-life.
- Produces less intense but more prolonged withdrawal symptoms than morphine.
- Use should be restricted to patients intolerant of morphine and should be closely monitored in the elderly and in patients with hepatic or renal dysfunction, all of whom are more likely to experience accumulation of the drug.
- There is potentially an increased risk of torsades de pointes or QT interval prolongation with methadone administration.
- Methadone is known to have several cytochrome P450-mediated drug interactions that may increase or decrease methadone levels. Methadone potentially has protein-binding interactions as well.
- Methadone should be used cautiously in patients whose compliance or communication with the prescribing clinician is in question, such as confused or demented patients.

Advantages of KADIAN® over Methadone

- The half-life of methadone varies from 15 to 55 hours depending on the individual. This variability of response between patients makes the duration of analgesia and dosing requirements difficult to determine. KADIAN® pharmacokinetics are predictable and titration is convenient.
- Deaths with methadone have increased in proportion to the increase in prescription methadone use, likely due to the unpredictable pharmacokinetics profile of the drug, including the delayed respiratory depression effects.
- KADIAN® dosing is q24h or q12h. Methadone is commonly dosed q8h to q6h. Methadone occasionally requires more frequent dosing than q6h.
- Sedation is more common with methadone than with morphine.
- Methadone side effects may not become apparent for weeks after starting the drug.
- Because of its association with addiction, many patients feel uncomfortable when filling prescriptions for methadone and some pharmacies are not willing to stock it.
- In many areas, methadone is only available as 10-mg tablets, so patients may need to take 8 or 10 tablets of methadone per day.
- KADIAN® is not metabolized by cytochrome P450 3A4 like methadone is, therefore avoiding potential drug interactions through this system.
- There is potentially an increased risk of torsades de pointes or prolongation of the QT interval with methadone administration.
- High protein binding of methadone makes it susceptible to protein-binding drug interactions.

OxyContin® (controlled-release oxycodone)

Oxycodone is a semi-synthetic opioid. Since 1994, it has been available as a long-acting medication (OxyContin®) that is dosed every 8 or 12 hours. The short-acting forms of oxycodone are usually manufactured in combination with acetaminophen (e.g. Percocet®, Tylox®, Roxicet®) or aspirin (e.g. Percodan®).

Indication

OxyContin® is indicated for around-the-clock management of moderate to severe pain when an analgesic agent is needed for an extended period of time.

Contraindications/Black box warnings:

OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin® Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. OxyContin® Tablets are NOT intended for use as a PRN analgesic.

OxyContin® 80 mg tablets are for use in opioid-tolerant patients only. This tablet strength may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin® tablets are to be swallowed whole and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed OxyContin® tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone.

Alcohol use warning: Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Pharmacology

Oxycodone is a potent semi-synthetic opioid agonist derived from morphine.

Table 11-5

Available OxyContin® Products		
Formulation	Products (Manufacturers)	Dosing Interval
Tablet, controlled-release	OxyContin® 5 mg, 10 mg, 20 mg, 40 mg, 80 mg Oxycodone Extended-Release Tablet 10 mg, 20 mg, 40 mg, 80mg	q8 to 12h

Delivery System

This formulation has a biphasic absorption pattern. OxyContin® is designed to deliver up to one-third of its contents in the first hour and then to slowly release the remainder over 8 to 12 hours. Because of this, it has a much quicker onset of action than some controlled-release medications. This may also explain the increase in side effects that sometimes occurs when patients are taking higher dosages of this medication. In addition, the initial OxyContin® drug release mimics short-acting medications. Short-acting medications should be reserved for PRN use. There is a trend towards eliminating short-acting medications in chronic pain treatment.

Dosing and Administration

The recommended starting dose of OxyContin® for opioid-naïve patients is 10mg every 12 hours. For patients already taking opioids, obtain the equivalent total daily dose of oral oxycodone from an equianalgesic dose table and round down to the closest tablet strength. OxyContin® is indicated for q12h dosing.

OxyContin® is not intended for use as a PRN analgesic. OxyContin® tablets must be swallowed whole and should not be broken, crushed, or chewed. Taking broken, chewed, or crushed controlled-release tablets leads to rapid release and absorption and is potentially fatal.

Pharmacokinetics

The absorption of oxycodone is greater than for morphine. Oxycodone is well absorbed from OxyContin® tablets with an oral bioavailability of 60% to 87%. In normal volunteers, the $t_{1/2}$ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin® exhibits a biphasic absorption pattern with two

apparent absorption half-times of 0.6 and 6.9 hours. This describes the initial release of oxycodone from the tablet followed by a prolonged release. The apparent elimination half-life of oxycodone after the administration of OxyContin® was 4.5 hours compared with 3.2 hours for immediate-release oxycodone.

Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Dose proportionality or bioavailability has been established for the 10-mg, 20-mg, 40-mg, 80-mg, and 160-mg strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC).

Oxycodone is a “pro-drug,” which means it must be metabolized by the liver in order to become effective. The liver enzyme responsible for this metabolism is cytochrome P450 2D6. Approximately 8% of whites, 3% of African Americans, and 1% of Asians are poor metabolizers of CYP2D6 and produce no CYP2D6 or undetectable levels of it. Poor metabolizers will experience little or no analgesia from oxycodone.

Oxycodone is metabolized primarily to oxymorphone and noroxycodone. Noroxycodone is the major circulating metabolite of oxycodone. Oxymorphone possesses analgesic activity but is present in low plasma concentrations.

Oxycodone and its metabolites are excreted primarily by the kidney.

Drug Interactions

Medications that interfere with cytochrome P450 2D6 liver enzyme (including some antidepressants such as Prozac® and Paxil®) (SSRI's), may reduce the effectiveness of oxycodone. Case reports in the literature support the clinical significance of these interactions (*see* appendix 11-2).

Side Effect Profile

- Same as for morphine.
- Oxycodone generally has fewer gastrointestinal side effects than morphine.

Advantages

- An effective oral opioid alternative to morphine for moderate to severe pain.
- Oxycodone may have fewer gastrointestinal side effects.

Disadvantages

- Deaths from overdose have been reported after misuse by crushing OxyContin® and thus destroying the delivery system.
- OxyContin® serum levels rise sharply in the first hour because of the early release of 33% of the dose. This peak may be associated with increased side effects, but faster relief of pain.
- The biphasic release of OxyContin® makes serum levels less stable than with other controlled-release opioids, which may result in uneven pain relief.
- Some patients are deficient in the cytochrome P450 2D6 enzyme required for oxycodone conversion to active metabolites. Other patients take medications that interact at the 2D6 site. As a result, neither patient population may be able to convert oxycodone to active drug.
- Many patients require q8h dosing with OxyContin® to maintain analgesic efficacy.

Advantages of KADIAN® over OxyContin®

- KADIAN® dosing is q24h or q12h. OxyContin® is dosed q12h. OxyContin® occasionally requires more frequent dosing than q8h.
- KADIAN® is not metabolized by cytochrome P450 3A4 like OxyContin®, therefore avoiding potential drug interactions through this system.
- Some patients may not be able to convert OxyContin® to active drug because of a deficiency of cytochrome P450 2D6 enzyme.
- OxyContin® has biphasic absorption with 33% of the drug being released within the first hour.
- OxyContin® is associated with a high rate of abuse.
- Because of the high street value of OxyContin®, patients may be at risk of having their medication stolen. Some pharmacies are no longer willing to stock OxyContin® because of the risk of armed robbery.

Long-Acting Morphine Product Comparison: MS Contin®, Oramorph SR®, Avinza®

MS Contin® (Purdue Pharma)

Indication

MS Contin® is indicated for the relief of moderate to severe pain. It is intended for use in patients who require repeated dosing with potent opioid analgesic over periods of more than a few days.

Contraindications/Black box warnings:

Ms Contin® contains morphine sulfate, an opioid agonist and a schedule II controlled substance, with an abuse liability similar to other opioid analgesics.

Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Ms Contin® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Ms Contin® tablets are a controlled-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Ms Contin® tablets are not intended for use as a PRN analgesic.

Ms Contin® 100 and 200 mg tablets are for use in opioid-tolerant patients only. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

Ms Contin® tablets are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed Ms Contin® tablets leads to rapid release and absorption of a potentially fatal dose of morphine.

Alcohol use warning: Morphine may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

Available Strengths

- Color-coded tablet in 5 strengths: 15 mg (blue), 30 mg (lavender), 60 mg (orange), 100 mg (gray), and 200 mg (green).
- Generic products are also available.

Delivery System

MS Contin® tablets are film-coated and contain wax-coated controlled-release granules of hydroxyalkyline cellulose to which morphine sulfate is absorbed. Gastric juices dissolve the tablet surface and expose the wax-coated granules. The wax coating slowly dissolves and exposes the cellulose carrying the morphine. Morphine then diffuses from the cellulose and is absorbed into the bloodstream. Thus, morphine release is controlled by means of the time it takes the tablet to disintegrate, the wax to dissolve, and the morphine to diffuse from the cellulose.

Dosage and Administration

MS Contin® is approved for 8-hour or 12-hour administration, but clinical experience suggests that 8-hour administration is necessary for some patients. There has been no systematic evaluation of MS Contin® as an initial opioid in the treatment of pain. Breakthrough pain may require supplementation with short-acting (immediate-release) morphine or shortening the dosing interval of MS Contin® to q8h.

Tablets should be swallowed whole and should not be broken, chewed, or crushed. The 200-mg tablets are for use in opioid-tolerant patients only.

Pharmacokinetics

The extent of absorption of MS Contin® is comparable with that of other morphine products but the rate is slower than oral immediate-release morphine sulfate. On average, 50% of absorption occurs in 1.5 hours. Food does not affect the bioavailability of the medication.

MS Contin® has a greater fluctuation in plasma morphine levels than KADIAN® (See Comparative Pharmacokinetics). The maximum plasma concentration is reached in 2.5 hours. Steady state is achieved in about one day.

Comparative Pharmacokinetics

Two important studies comparing the pharmacokinetics of KADIAN® with MS Contin® have been completed by Gourlay and colleagues: one involving once-a-day dosing and one involving twice-a-day dosing. Both studies were conducted in patients with cancer pain after a lead-in period in which the dose of morphine was stabilized at an effective dose. The data from the once-a-day study are presented below. These data show that KADIAN® has fewer fluctuations in plasma concentration than does MS Contin®.

Study Design and Population

The study was a randomized, double-blind, double-dummy, 2-treatment, 2-crossover study with a lead-in period. Twenty-four patients with moderate to severe cancer pain completed the study. After a lead-in period to achieve stabilization at an effective dose, patients were randomly assigned to receive either KADIAN® q24 hr or MS Contin® q12 hr. Blood samples were drawn on the last day of each treatment period. All doses were corrected to 100mg for comparison purposes. The study parameters are listed in Table 11-3.

Table 11-6

Mean Steady-State Pharmacokinetic Parameters for Morphine Following KADIAN® or MS Contin® (AUC, C_{max} , C_{min} corrected to 100 mg dose)		
Parameter	KADIAN® q24h	MS Contin® q12h
AUC (ng/ml)/h	500.9 + 193.2	457.3 + 184.7
C_{max} (ng/ml)	37.3 + 14.0	36.9 + 15.5
C_{min} (ng/ml)	9.9 + 5.2*	7.6 + 4.6
t_{max} (h)	10.3 + 3.3*	4.4 + 2.3
$t > 0.75 C_{max}$ (h)	6.0 + 3.0*	4.8 + 2.8
Fluctuation	1.4 + 0.4*	1.6 + 0.5

*Statistically significantly different from MS Contin® q12h ($p < 0.05$ by ANOVA)

Study Results

Dose normalization to 100 mg permitted a direct comparison of the pharmacokinetics parameters of the 2 formulations. The differences in AUC values were not statistically significant, which indicates that the extent of absorption from the 2

products is similar. The C_{\max} values were also similar. However, the other pharmacokinetics parameters differed significantly.

KADIAN® exhibited a higher C_{\min} and less fluctuation in plasma morphine concentrations. A longer time to maximum plasma concentration (t_{\max}) was observed with KADIAN®. KADIAN® has a longer time that the plasma concentration remained about 75% of the C_{\max} when compared with MS Contin®, as well. The authors concluded that KADIAN® given once daily has a superior pharmacokinetic profile when compared with MS Contin® twice daily.

Advantages of KADIAN® over MS Contin®

- KADIAN® allows dose titration at lower doses in 10-mg increments.
- KADIAN® is approved for sprinkle and G-tube administration. MS Contin® tablet technology does not allow this type of administration.
- Labeling supports the use of MS Contin® q12h to q8h. KADIAN® is rarely dosed more than q12h in clinical practice.
- KADIAN® 10-mg and 20-mg formulations allow a physician to begin therapy at a lower dose than the 30-mg lowest strength of MS Contin®.
- KADIAN® provides steady and consistent blood plasma concentrations with less fluctuation than MS Contin®.
- KADIAN® exhibits a higher C_{\min} and less fluctuation in plasma morphine concentrations than MS Contin® does. A longer time to maximum plasma concentration (t_{\max}) was observed with KADIAN®. In addition, KADIAN® has a longer time that the plasma concentration remains above 75% of the C_{\max} when compared with MS Contin®. KADIAN® given once daily has a superior pharmacokinetic profile when compared with MS Contin® twice daily (Gourlay et al, 1997).

Comparative Clinical Efficacy

Two double-blind, multiple-dose, active controlled studies of the efficacy of KADIAN® in patients with cancer pain have been carried out. Gourlay et al (1997) evaluated KADIAN® q24h versus MS Contin® q12h. Broomhead et al (1997) evaluated KADIAN® administered q24h versus KADIAN® administered q12 h versus MS Contin® q12h.

Neither study showed a statistical difference in pain control or the occurrence of breakthrough pain (as evidenced by the percentage of patients requiring rescue

medication and the timing of rescue medication) between KADIAN® administered once or twice daily and MS Contin® administered q12h.

The 1997 Gourlay et al study also evaluated patient preference for KADIAN® q24h versus MS Contin® q12h and found there were no statistically significant differences in patient preference ratings between the 2 treatment groups.

Patient preference for once-daily KADIAN® or twice-daily MS Contin® were evaluated in an open label study of the two formulations in patients with cancer pain by Kerr and Tester in 2000. In this study there was a clear preference for KADIAN® q24h over MS Contin® q12h. Of the 104 patients for whom evaluative data were available, 57 (55%) preferred KADIAN® q24h, 34 (33%) preferred MS Contin®, and 13 (12%) had no preference. A clear patient preference for KADIAN® daily over MS Contin® q12h was identified in this study.

Oramorph SR® (Roxane Labs)

Indication

Oramorph SR® is indicated for the relief of pain in patients who require opioid analgesics for more than a few days.

Contraindications/Black box warnings:

This is a sustained release dosage form. Patient should be instructed to swallow the tablet as a whole; the tablet should not be broken in half, nor should it be crushed or chewed.

The sustained release of morphine from Oramorph SR should be taken into consideration in event of adverse reactions or overdose.

In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of an opioid antagonist in such a person should be avoided. If necessary to treat serious respiratory depression in a physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Alcohol use warning: Morphine should not be taken with alcohol or other CNS depressants (sleep aids, tranquilizers) because additive effects, including CNS depression, may occur. A physician should be consulted if other prescription and/or over-the-counter medications are currently being used or are prescribed for future use.

Precautions

Contraindications for Oramorph SR® are similar to those for immediate-release morphine, with the addition of paralytic ileus.

Available Strengths

- White tablet embossed in 4 strengths: 15 mg, 30 mg, 60 mg, 100 mg.

Delivery System

Oramorph SR® tablets contain sustained-release granules of hydroxypropyl methylcellulose to which morphine sulfate is adsorbed. Gastric juices dissolve the tablet surface and expose the coated granules. The coating slowly dissolves and exposes the cellulose carrying the morphine. Morphine then diffuses from the cellulose and is absorbed into the bloodstream.

Dosage and Administration

Oramorph SR® is approved for administration every 12 hours. The dosing interval should not be extended beyond 12 hours or shortened to less than 8 hours. The 30-mg tablet strength is recommended for the initial titration period for patients with a daily morphine requirement of 120mg or less. For patients with low daily morphine requirements, the 15-mg tablet should be used. There has been no systematic evaluation of Oramorph SR® as an initial opioid in the treatment of pain. Tablets should be swallowed whole and should not be broken, chewed, or crushed.

Oramorph SR® has not been evaluated in children and therefore its use in the pediatric population is not recommended.

Pharmacokinetics

The pharmacokinetics of Oramorph SR® show considerable intersubject variation. For example, time to peak plasma concentrations averages around 4 hours. The range for this average varies from 1 hour to 7 hours. However, there are fewer fluctuations

between single-dose peak plasma morphine concentrations compared with immediate-release morphine. Steady-state plasma concentrations are achieved in 1 to 2 days.

The extent of absorption of Oramorph SR® is comparable with that of other morphine products but the rate is slower than oral immediate-release morphine sulfate. On average, 50% of absorption occurs in 1.5 hours. Oramorph SR® does not release morphine continuously over the course of the dosing interval. The possible effect of food on bioavailability has not been evaluated. Dose proportionality or bioavailability has not been established for currently available strengths.

Advantages of KADIAN® over Oramorph SR®

- Titration is more difficult with 15, 30, 60, and 100 mg Oramorph SR®. KADIAN® allows dosing titration in 10-mg increments at some doses.
- KADIAN® is approved for sprinkle and G-tube administration. Oramorph SR tablet does not allow this type of administration.
- Clinical practice supports the use of Oramorph SR® q12h to q8h. KADIAN® is rarely dosed more than q12h in clinical practice and pharmacokinetically does not require more frequent dosing.

Avinza® (King Pharmaceuticals)

Indication

Avinza® is indicated for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time.

Contraindications/Black box warnings:

Avinza® capsules are to be swallowed whole or the contents of the capsules sprinkled on applesauce. The capsule beads are not to be chewed, crushed, or dissolved due to the risk of rapid release and absorption of a potentially fatal dose of morphine.

Patients must not consume alcoholic beverages while on Avinza® therapy. Additionally, patients must not use prescription or non-prescription medications containing alcohol while on Avinza® therapy. Consumption of alcohol while taking Avinza® may result in the rapid release and absorption of a potentially fatal dose of morphine.

Alcohol use warning: Morphine may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression. In vitro studies performed by the FDA demonstrated that when Avinza® 30 mg was mixed with 900 mL of buffer solutions containing ethanol (20% and 40%), the dose of morphine that was released was alcohol concentration-dependent, leading to a more rapid release of morphine. While the relevance of in vitro lab tests regarding Avinza® to the clinical setting remains to be determined, this acceleration of release may correlate with in vivo rapid release of the total morphine dose, which could result in the absorption of a potentially fatal dose of morphine.

Precautions

Contraindications are similar to those for immediate-release morphine, with the addition of gastrointestinal obstruction, particularly paralytic ileus. Caution should be used when administering Avinza® within 24 hours of cordotomy or similar surgery.

Available Strengths

Color-coded gelatin capsules in 4 strengths: 30 mg (yellow), 60 mg (bluish-green), 90 mg (red), and 120 mg (blue-violet).

Delivery System

Avinza® capsules contain polymer-coated, sustained-release beads of morphine sulfate. The capsules use the proprietary SODAS (Spheroidal Oral Drug Absorption System) technology to produce an extended-release component of Avinza®. As the capsule passes through the GI tract, soluble polymers of ammoniomethacrylate dissolve, leaving pores within the outer membrane. Fluid enters the core of the beads and dissolves the drug. The resultant solution diffuses out in a controlled, predetermined manner allowing for prolongation of the dissolution phase.

The diffusion of the dissolved solution within the beads is mediated by fumaric acid, which acts as an osmotic agent and a local pH modifier. Fumaric acid increases the acidity of the drug (decreases the pH) and serves as an osmotic agent that controls the rate of osmotic diffusion. Fumaric acid is used in small amounts as a food additive to increase acidity. The safety of large amounts of fumaric acid (as are found in doses of Avinza® over 1600mg/day) has not been established. Large doses of fumaric acid may result in serious renal toxicity. In rats, fumaric acid monoethylester leads to

concentration defects (during water deprivation) and reduced glomerular filtration rates (Hohenegger, 1989).

Dosage and Administration

Avinza® should not be given more frequently than every 24 hours. The 30-mg capsule strength is recommended for the initial titration period. There has been no systematic evaluation of Avinza® as an initial opioid in the treatment of pain, although efficacy studies have included patients in the study population who were not previously taking opioids. Capsules should be swallowed whole and should not be broken, chewed, or crushed. Doses above 1600mg per day contain a quantity of fumaric acid that has not been shown to be safe and that may result in serious renal toxicity.

As alternatives to ingesting whole capsules, capsules may be opened and the beads ingested with a small amount of applesauce (sprinkle administration).

The safety and effectiveness of Avinza® in pediatric patients below the age of 18 years have not been established. The range of dose may not be appropriate for this patient population. Sprinkle administration is not a suitable alternative for these patients.

Side Effect Profile

In controlled trials for malignant and nonmalignant pain, the most serious adverse events reported with administration of Avinza® were vomiting, nausea, death, dehydration, dyspnea, and sepsis. Deaths occurred in patients treated for pain due to underlying malignancy. The common adverse events seen on morphine initiation are similar to those for other opioid products.

Pharmacokinetics

Avinza® consists of two components, an immediate-release component that rapidly achieves plateau morphine concentrations and an extended-release component that maintains plasma concentrations throughout the 24 hour dosing interval. The extent of absorption is comparable with that of other extended-release morphine formulations. Bioavailability is not affected by presence of food. Dose proportionality has been established in chronic pain patients over the range of 30 to 180mg.

The maximum plasma concentration of Avinza® is achieved in 0.5 hours after oral administration. Steady-state plasma concentrations are reached in 2 to 3 days.

Advantages of KADIAN® over Avinza®

- The KADIAN® 10-mg formulation allows clinicians to begin therapy at a lower dose than the 30-mg lowest strength of Avinza®.
- Avinza® is only indicated for q24h dosing. KADIAN® allows the flexibility of q24h and q12h dosing.
- KADIAN® allows dosing titration in 10-mg increments.
- Avinza® is not approved for G-tube administration.
- The dose of Avinza® is limited to 1600 mg per day due to potential renal toxicity from the fumaric acid component. KADIAN® does not contain fumaric acid.
- Avinza® contains an immediate-release component that peaks in 0.5 hours. This mimics short-acting medications. Short-acting medications should be reserved for PRN use. In addition, there is a trend towards eliminating short-acting medications in chronic pain treatment.

Summary of KADIAN® Advantages

Contains morphine in an oral formulation:

- The oral route is recommended by the World Health Organization for treatment of pain.
- The oral route has a more rapid onset of analgesic action than does transdermal delivery (advantage vs. Duragesic®).
- No maximum dose (advantage vs. Avinza®).
- Easily titratable (advantage vs. Duragesic® and Methadone).
- Titration can occur in 10-mg increments at lower doses when small increases in the dose are more likely to be needed (advantage vs. MS Contin®, Oramorph SR®, and Avinza®).
- Known manageable side effects.
- No special patient education required before administration of KADIAN®

(advantage vs. Duragesic®).

Desirable Pharmacokinetic Profile

- KADIAN® does not require cytochrome P450 2D6 for conversion to active drug (advantage vs. OxyContin®).
- KADIAN® is not metabolized by the cytochrome P450 system, therefore avoiding potential drug interactions through this system (advantage vs. Duragesic®, OxyContin®, and Methadone).
- KADIAN® pharmacokinetics are predictable and titration is convenient (advantage vs. Duragesic® and Methadone).
- KADIAN® has no risk of torsades de pointes (advantage vs. Methadone).
- KADIAN® does not have a short-acting component (advantage vs. OxyContin® and Avinza®).
- Easy to manage at home – less restrictive and invasive than parenteral therapy.
- KADIAN® is more cost-effective in terms of savings in nursing time vs. infusion devices. KADIAN® requires less nursing time for administration than Duragesic®.

Has a capsule formulation:

- Tasteless (advantage vs. morphine solution).
- KADIAN® has not been associated with a dramatic increase in death rate from overdose (advantage vs. Methadone).

Is an extended-release formulation:

- Allows the option of dosing every 24 hours and should not require dosing more often than q12h (advantage vs. OxyContin®, Methadone, MS Contin®, and Oramorph SR®).
- KADIAN® given once daily has a superior pharmacokinetic profile when compared with MS Contin® twice daily (Gourlay 1997).
- Can be given without regard to meals.
- Capsule can be opened and the pellets sprinkled on small amount of applesauce for ingestion (advantage vs. Duragesic®, Methadone, OxyContin®, MS Contin®, and Oramorph SR®).
- The KADIAN® capsule can be opened and the pellets mixed with a small

amount of water and administered through a 16-French (or larger) G-tube (advantage vs. Duragesic®, Methadone, OxyContin®, MS Contin®, Oramorph SR®, and Avinza®).

Is formulated for dosing every 24 hours:

- Reduced dosing frequency relative to immediate-release morphine tablets or solution and some controlled-release formulations (MS Contin®, Oramorph SR®, OxyContin®, and Methadone).
- Patient preference for KADIAN® q24h over MS Contin® q12h has been documented in clinical trials (Kerr and Tester 2000).
- May facilitate uninterrupted sleep for some patients (advantage vs. MS Contin®)

Is available in 8, easily discernible, color-coded strengths:

- Eight strengths allow precise dosage: 10 mg (light blue), 20 mg (yellow), 30 mg (blue-violet), 50 mg (blue), 60 mg (pink), 80 mg (light orange), 100 mg (green), and 200 mg (brown).

Possible Objections to KADIAN®

Versus other Morphine Preparations

- Breakthrough pain requires therapy with immediate-release morphine preparations (also true of other controlled-release opioid products).
- Perceived as expensive compared with oral morphine sulfate solution and generic MS Contin®. Depending on total number of daily doses of the other products, KADIAN® may be comparable in price. Education is required regarding cost-effectiveness.

Versus Nonopioid Preparations

- Fear of the use of opioids among medical practitioners and patients; the market requires education.
- Adverse effects of morphine require use of other medications, e.g., prophylaxis for constipation. This is inconvenient and adds to costs.
- Morphine is a regulated substance and its usage introduces prescribing complications for clinicians.

Summary

- Extended- and controlled-release morphine preparations occupy a variable share of the oral morphine market. Of the extended- and controlled-release preparations presently on the market, MS Contin® is the longest established and OxyContin® is the most widely used. All of the extended- and controlled-release formulations of morphine, oxycodone, and transdermal fentanyl are suitable for relief of chronic cancer and nonmalignant moderate to severe pain.
- The advantages of the extended-release preparation KADIAN® can be summarized as follows:
- KADIAN® is suitable for administration every 12 to 24 hours, whereas the recommended dosing interval for MS Contin® is every 8 to 12 hours and OxyContin® is every 12 hours. Avinza® is every 24 hrs.
- KADIAN® has been shown to be as effective as 4-hour immediate-release morphine formulations and 12-hour controlled-released morphine tablets for relief of moderate to severe chronic pain.
- KADIAN® can be administered by opening the capsule and sprinkling the pellets on a small amount of applesauce. Also, the pellets can be mixed with a small amount of water and administered through a 16-French (or larger) G-tube.
- KADIAN® has fewer fluctuations in plasma concentrations.

Literature Cited

- Broomhead A, Kerr R, Tester W, et al. Comparison of a once-a-day sustained-release morphine formulation with standard oral morphine treatment for cancer pain. *J Pain Symptom Manage.* 1997;14:63-73.
- Hohenegger M, et al. Nephrotoxicity of fumaric acid monoethylester (FA ME). *Adv Exp Med Biol.* 1989;252:265-272.
- Kerr RO, Tester WJ. A Patient Preference Study Comparing Two Extended-Release Morphine Sulfate Formulations (Once-Daily Kadian(R) versus Twice-Daily MS Contin(R)) for Cancer Pain. *Clinical Drug Investigation.* 2000;19:25-32.
- Sims SA, Snow LA, Porucznik CA. Surveillance of methadone-related adverse drug events using multiple public health data sources. *J Biomed Inf.* 2007;40:382-389.

Table 11-7 REFERENCE - LONG-ACTING OPIOID COMPARISON TABLE

	KADIAN®	OxyContin®	MS Contin®	Duragesic®	Avinza®	Methadone
Dosing	10, 20, 30, 50, 80, 60, 100, 200 mg QD or BID	10, 20, 40, 80 mg BID*	15, 30, 60, 100, 200 mg BID*	25, 50, 75, 100 mcg 72hrs.*	30, 60, 90, 120 mg QD (1600/day max)	5, 10, 40 mg, q6-8h (dosing varies)
Monophasic vs. Biphasic Absorption	Monophasic	Biphasic	Monophasic	Monophasic	Biphasic	Monophasic
Technology	Polymer-coated pellets	Matrix	Matrix	Reservoir patch (transdermal)	Copolymer beads (fumaric acid)	Immediate-release long half-life drug
Metabolism	M3G & M6G glucuronide metabolites	P450	M3G & M6G glucuronide metabolites	P450 3A4 isoenzyme	M3G & M6G glucuronide metabolite	CYP1A2, 2D6, and 3A 3/4 enzyme substrate; CYP2D6 enzyme inhibitor
Most Common Adverse Events	Drowsiness, constipation, nausea, dizziness, anxiety (<10%)	Constipation, nausea, somnolence, dizziness, pruritus, vomiting	Constipation, dizziness, sedation, nausea, vomiting, dysphoria, euphoria	Nausea, vomiting, constipation, dry mouth, somnolence, confusion (<10%)	Vomiting, nausea, death, dehydration, dyspnea, sepsis	Lightheadedness, dizziness, drowsiness, nausea, vomiting, constipation, hypotension, weakness (<10%)
Titration	24-48 h	24-48 h	24-48 h	72 h	24-48 h	q48-72h once stable (stability achieved in 3 to 5 days)
Plasma Fluctuations	Steady-state, no bolus	Bolus	Peaks & trough	Steady	Bolus	Steady
Routes	Oral, sprinkle, G-tube	Oral	Oral	Patch	Oral, sprinkle	Oral

*Refer to the Royal Abstract (see Appendix 11-1) for information on dosing in clinical practice.

Self-Assessment Test

Circle the best response

- 1) Which of the following statements support morphine as the gold standard potent opioid for the treatment of pain?
 - a. 60% to 85% of patients respond adequately to regular administration of morphine.
 - b. Morphine is available orally, parenterally, and transdermally.
 - c. Morphine has a ceiling effect.
 - d. Morphine has known and predictable side effects.

- 2) Which of the following is a potential drawback compared with morphine for the use of methadone in the continuous treatment of chronic cancer pain?
 - a. Repeated administration of methadone could lead to accumulation of the drug.
 - b. Methadone produces more intense and more prolonged withdrawal symptoms than does morphine.
 - c. Methadone has not been shown to have as much analgesic efficacy as morphine.
 - d. Methadone causes more pruritus than does morphine.

- 3) Which of the following statements is true regarding mixed agonist-antagonists?
 - a. Mixed agonist-antagonist enhance analgesic efficacy when given in conjunction with a mu agonist.
 - b. Mixed agonist-antagonists have a lower risk of psychotomimetic effects.
 - c. Mixed agonist-antagonists are recommended for use in chronic pain because of their good side effect profile.
 - d. Mixed agonists-antagonists potentially reduce analgesia or precipitate withdrawal symptoms when administered to patients taking mu agonists.

- 4) Which of the following statements is true regarding Duragesic®?
 - a. Onset of analgesic activity is delayed by 6 hours.
 - b. Duragesic® patches may be changed every 48 hours.
 - c. Duragesic® is easily titratable.

- d. Fentanyl levels clear quickly after removal of the Duragesic® patch.

- 5) Which of the following is not an advantage of KADIAN®?
- KADIAN® can be given without regard to meals.
 - KADIAN® allows more flexibility in dosing intervals than do other morphine formulations.
 - KADIAN® can be administered by G-tube.
 - KADIAN® delivers medication up to 24 hours.
 - All of the above are advantages.
- True or False**
- 6) Methadone is effective in suppressing withdrawal symptoms in patients with opioid dependency.
- True
False
- 7) The extent of KADIAN® absorption is unaffected by the presence of food.
- True
False
- 8) MS Contin® has a C_{min} that is similar to that of KADIAN®.
- True
False
- 9) KADIAN® contraindications and warnings are generally the same as for morphine except that KADIAN® is contraindicated in paralytic ileus and GI obstruction.
- True
False
- 10) KADIAN® and OxyContin® both exhibit biphasic absorption.
- True
False

Answers to Self-Assessment Test

1. d	6. a
2. a	7. a
3. d	8. b
4. b	9. a
5. e	10. b

Appendix 11-1: Royal Abstract

Clinical practitioners often use long-acting opioids more often than indicated. There are several reasons for this practice. The primary reason is that patients experience pain at the end of many recommended dosing intervals. Some practitioners believe that many patients actually use breakthrough doses of instant-release medication to provide pain relief during the interval between long-acting doses, rather than for true breakthrough pain. This end-of-dose pain can be reduced by increasing the number of daily doses of controlled-release medication. An additional (although theoretical) advantage is that blood levels often vary less with more frequent dosing.

Recently, a professor of Internal Medicine and Anesthesiology/Pain Management at the University College of Medicine in Oklahoma collected data to support this practice.

A retrospective chart review was performed evaluating the use of various long-acting opioid preparations, including Duragesic®, MS Contin®, KADIAN®, OxyContin®, and methadone. The purpose of the review was to determine the percentage of patients who required more frequent dosing than the labeling for each opioid. Three hundred and sixty charts were reviewed. Primary pain diagnoses varied from nociceptive to neuropathic pain. The use of immediate-release morphine (MSIR) for breakthrough pain was also evaluated.

The review found that patients often used long-acting opioid formulations more frequently than recommended by manufacturers. Of the oral formulations, KADIAN® was most likely to be dosed either QD or BID (94.2%), whereas MS Contin® and OxyContin® were dosed more frequently than BID in 70.5% and 87.2%, respectively. Nearly one-fourth of patients taking Duragesic® required q48h dosing. KADIAN® maintained a less frequent dosing schedule than other extended-release opioid preparations. In addition, breakthrough medication requirements were reduced with KADIAN®.

Table 11-8

Frequency of Dosing for Common Long-Acting Opioids						
	Total # of Patients	QD%	BID%	TID%	QID	MSIR% (breakthrough)
Duragesic®	77	NA	72 hr 76.6	48 hr 23.4		58.4
Ms Contin®	68	1.5	27.9	67.6	2.9	48.5
KADIAN®	69	60.9	33.3	2.9	2.9	43.5
OxyContin®	86	0	12.8	59.3	27.9	57.0
Methadone	60	0	11.7	28.3	60.0	56.7

Royal M, Jensen M, Gunyea I, et al. Retrospective assessment of the frequency of dosing of sustained-release opiate preparations in chronic pain patients. 2002.

Appendix 11-2: Substrates and Inhibitors of Cytochrome P450 Subtypes

Many drugs (and other chemicals, including toxins) undergo enzymatic biotransformation in the liver. The transformation may activate or deactivate the drug, depending on the chemical structure of the drug. The major group of enzymes responsible for drug biotransformation in the liver is the cytochrome P450 monooxygenase system of enzymes. These are often called the P450 or CYP 450 enzymes, for short. There are a number of individual enzymes in the CYP group, including 2D6, 3A4, and 1A2, which are important in this process, although 3A4 is the most commonly involved in drug metabolism.

It is important to know which drugs are metabolized by the P450 system because the system can be saturated. If the system is saturated by a drug or other substrate (the material that is transformed by the enzymes), it is not available to metabolize other drugs. That can lead to either a lack of activated forms of the drug (if P450 enzymes activate that drug) or excessive levels of the drug (if P450 enzymes deactivate the drug). It is not always predictable which drug will have excessive or insufficient levels if more than one drug that affect this system is given.

The P450 system can also be induced, which means its activity levels can be increased by chronic exposures to substances, such as with chronic drug therapy. In those cases, the P450 system becomes more active, resulting in excessive or

insufficient drug levels, depending on whether the system deactivates or activates a particular drug.

The prescribing information on drugs that are affected by the P450 system includes detailed information on the effects of the P450 system on that particular drug and also includes a list of other drugs that are expected to be affected if the patient is taking them concurrently.

KADIAN® does not invoke the P450 system, but rather is metabolized to morphine-6-glucuronide through glucuronidation. This means that it is not as complicated for the clinician to determine what drugs might cause alterations in the drug levels of KADIAN® and it is not as complicated to predict how the pharmacodynamics of other drugs a patient is taking would be affected.

CYP2D6

Substrates

METHADONE

OXYCODONE

Antidepressants

Amitriptyline (Elavil)

Clomipramine

(Anafranil) Desipramine

(Norpramin) Doxepin

(Adapin, Sinequan)

Fluoxetine (Prozac)

Imipramine

(Tofranil)

Nortriptyline

(Pamelor) Paroxetine

(Paxil)

Venlafaxine (Effexor)

Antipsychotics

Haloperidol (Haldol)

Perphenazine (Etrafon,

Trilafon) Risperidone

(Risperdal)

Thioridazine (Mellaril)

Beta blockers

Metoprolol

(Lopressor)

Penbutolol (Levatol)

Propranolol (Inderal)

Timolol (Blocadren)

Opioids

Codeine, tramadol (Ultram)

***Inhibitors (decrease
metabolism of substrates)***

Antidepressants

Paroxetine (Paxil)

Fluoxetine (Prozac) Sertraline

(Zoloft) Fluvoxamine

(Luvox) Nefazodone

(Serzone)

Venlafaxine (Effexor)

Clomipramine (Anafranil)

Amitriptyline (Elavil)

Antipsychotics

Fluphenazine (Prolixin)

Haloperidol (Haldol)

Perphenazine (Etrafon,

Trilafon) Thioridazine

(Mellaril)

Cimetidine (Tagamet)

CYP3A4

Substrates

FENTANYL
 METHADONE
 Antidepressants
 Amitriptyline (Elavil)
 Imipramine (Tofranil)
 Sertraline (Zoloft)
 Venlafaxine (Effexor)
 Nefazodone (Serzone)
 Benzodiazepines
 Bupropion (Wellbutrin)
 Alprazolam (Xanax)
 Triazolam (Halcion)
 Midazolam (Versed)
 Calcium blockers
 Carbamazepine (Tegretol)
 Cisapride (Propulsid)
 Dexamethasone (Decadron)
 Erythromycin
 Ethinyl estradiol
 (Estraderm, Estrace)
 Glyburide (Glybna, Glyburide)
 Micronase)
 Ketoconazole (Nizoral)
 Lovastatin (Mevacor)
 Terfenadine (Seldane)
 Astemizole (Hismanal)
 Verapamil (Calan, Isoptin)
 Testosterone
 Theophylline
 Protease inhibitors (HIV agents)
 Ritonavir (Norvir)
 Saquinavir (Invirase)
 Indinavir (Crixivan)
 Nelfinavir (Viracept)

Inhibitors

Antidepressants
 Nefazodone (Serzone)
 Fluvoxamine (Luvox)
 Fluoxetine (Prozac)
 Sertraline (Zoloft)
 Paroxetine (Paxil)
 Venlafaxine (Effexor)
 Azole antifungals
 Ketoconazole (Nizoral)
 Itraconazole (Sporanox)
 Fluconazole (Diflucan)
 Cimetidine (Tagamet)
 Clarithromycin (Biaxin)
 Diltiazem
 Erythromycin
 Protease inhibitors

Inducers increase metabolism of substrates)

Carbamazepine
 Dexamethasone
 Phenobarbital
 Phenytoin (Dilantin)
 Rifampin (Rifadin, Rimactane)

CYP1A2

Substrates

METHADONE

Antidepressants

Amitriptyline (Elavil)

Clomipramine (Anafranil)

Clozapine (Clozaril)

Imipramine (Tofranil)

Other

Propranolol (Inderal)

R-warfarin

Theophylline

Tacrine (Cognex)

Inducers

Omeprazole (Prilosec)

Phenobarbital

Phenytoin (Dilantin)

Rifampin (Rifadin, Rimactane)

Smoking

Charcoal-broiled meat

Inhibitors

Fluvoxamine (Luvox)

Grapefruit juice

Quinolones

Ciprofloxacin (Cipro)

Enoxacin (Penetrex) > norfloxacin

(Noroxin) >

Ofloxacin (Floxin) > lomefloxacin

(Maxaquin)



CHAPTER TWELVE



Clinical Research Papers

Learning Objectives

After reading this chapter, you should be able to:

- List and describe the phases of the Pharmaceutical Investigation.
- Describe the anatomy of a clinical research paper and the importance of each part.

Terminology

Exclusion criteria:	variables used to eliminate patients from the study.
Inclusion criteria:	variables used to define the patient population.
<i>n</i>:	the number of patients participating in the experiment.
Reliability:	a measure of the extent to which the experiment produces the same result.
Validity:	extent to which the experiment measures the specified objectives.
Variance:	extent to which variables or characteristics of the subject population differ.
Randomization:	a selection procedure used to eliminate the bias in a subject population.
Placebo:	pharmacologically inactive pill.
Open label:	both patient and physician are aware of actual treatment.
Single blind:	only the physician is aware of actual treatment.
Double blind:	neither the patient nor the physician is aware of actual treatment.
Single group:	one subject group with one treatment.
Multiple group:	one or more subject groups (usually one group is a control group).
Parallel group:	two or more subject groups studied simultaneously.
Crossover group:	each subject is given each treatment (double crossover repeats crossover design).
Objective criteria:	clearly defined variables with exact measurements. <i>Example: visual and numeric analog pain scales.</i>
Subjective criteria:	variables that are less well defined (typically exhibiting great inpatient differences). <i>Example: patient self-report.</i>

Introduction

Reviewing the investigation and anatomy of clinical research papers will facilitate an understanding of the general information that a clinical study provides. This chapter reviews the phases of pharmaceutical investigation and the anatomy of clinical research papers.

Phases of Pharmaceutical Investigation

Preclinical

- Evaluation of animal and *in vitro* pharmacology.

Phase I

- Evaluation of safety in healthy humans.
- Determination of dose.
- Evaluation of human pharmacology.

Phase II

- Clinical evaluation of specific patient population.

Phase III

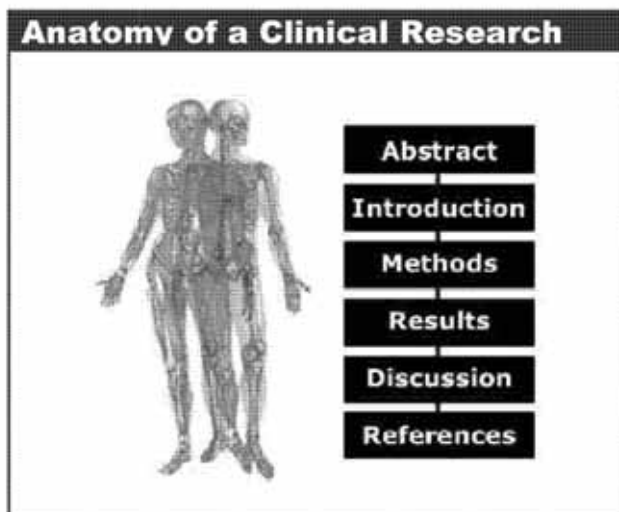
- Evaluation of safety and efficacy in larger numbers of patients.

Phase IV

- Postmarketing evaluation with larger population.

Anatomy of a Clinical Research Paper

Figure 12-1



Abstract

A brief summary of the study.

- **Key Information**
- Abstract provides directions for navigating the study.
- Contains purpose statement, information about methods, results, discussion.

Introduction

The introduction section reviews information about the subject and establishes the purpose for the study.

Methods

The methods section describes what procedures and designs were used in conducting the research.

- **Key Terms**
- **Reliability-** a measure of the extent to which the experiment produces the same result.

- **Validity**- extent to which the experiment measures the specified objectives.
- Patient Population
- *n*- the number of patients participating in the experiment.
- **Inclusion criteria**- variables used to define the patient population.
- **Exclusion criteria**- variables used to eliminate patients from study.
- **Variance**- extent to which variables or characteristics of the subject population differ.

- **Control Methods**
- **Randomization**- a selection procedure used to eliminate the bias in a subject population.
- **Placebo** - pharmacologically inactive pill.
- **Open label** - both patient and physician are aware of actual treatment.
- **Single blind** - only the physician is aware of actual treatment.
- **Double blind**- neither the patient nor the physician is aware of actual treatment.

- **Experimental Design**
- **Single group** - one subject group with one treatment.
- **Multiple group** - one or more subject groups (usually one group is a control group).
- **Parallel group** - two or more subject groups studied simultaneously.
- **Crossover group** - each subject group is given each treatment (double crossover repeats crossover design).

- **Measurement Parameters**
- **Objective criteria** - clearly defined variables with exact measurements. Example: visual and numeric analog pain scales.
- **Subjective criteria**- variables that are less well defined (typically exhibiting great inpatient differences). Example: patient self-report.

Results

The results section of the study reports the collected data and emphasizes the statistical significance of the findings (also used to state means, standard deviation, etc.).

Discussion

The discussion portion of the study is used to interpret the value and applications of the results.

References

The reference section of the study contains documentation for sources of information.

Glossary

Absorption:	The taking in or assimilation of a substance (e.g., a drug or food) into body tissues.
Abuse :	The use of a prescription medication in a manner other than that for which it was prescribed. This can include recreational use of a prescription drug.
Acetylcholine:	Neurotransmitter at cholinergic synapses in the central sympathetic, and parasympathetic nervous systems.
Acidic:	A pH less than 7.0
Action potential:	Short-lived electrical nerve impulse, created when a neuron is stimulated. The impulse spreads like a wave along the length of the nerve cell.
Acupuncture:	A procedure that originated in Far Eastern medical traditions that involves inserting needles into specific locations of the body to relieve pain and other symptoms. This is different than dry needling and moxibustion.
Acute pain:	Short-term pain experienced after surgery or a traumatic injury
Acute:	Having a short course.
Addiction:	(see Psychological dependence)
Addison's disease:	A deficiency of the adrenal cortex and therefore the hormones produced in this area.
Adenoma:	Benign tumor which arises from or resembles glandular tissue.
Adjuvant:	Adjuvant drugs are medications that are not analgesics, but that may reduce pain or improve other symptoms associated with chronic pain. The term adjuvant itself means an aid or assistant and the adjuvant drug is typically given as an additional medication to augment pain control.
Adsorption:	A process by which a thin layer of a material is attached to another, as when molecules of medication are attached to beads. This term is similar in spelling, but different in meaning, to the more familiar term, absorption.
Afferent:	Conducting toward the center (e.g., sensory nerve).
Affinity:	Goodness of fit.
Agonist:	Drug that binds to and stimulates physiological activity at cell receptors normally stimulated by naturally occurring substances.
Agonist-antagonist:	Medication that has one effect at low doses and a different effect at higher doses. For example, at low doses, the drug may act as an agonist, but acts as an antagonist at higher doses. Example: Buprenorphine
Alkaline:	A pH greater than 7.0
Allergy:	Unusual hypersensitivity when exposed to a particular substance (allergen).
Allodynia:	Condition in which ordinarily nonpainful stimulus evokes pain.
Amblyopia:	Weakness in vision in one eye that can cause it to relax and drift relative to the other (also called lazy eye).
Ambulatory:	Walking or able to walk.
Amenorrhea:	Lack of menstrual periods.
AMES test:	A test for potential carcinogenic properties of a drug. It uses the rate of genetic mutations caused in a strain of the bacterium Salmonella.

Amphetamine:	Powerful synthetic central nervous system stimulant.
Amylase:	An enzyme that occurs in saliva and pancreatic juice and aids the digestion of starch. Amylase will also hydrolyze glycogen to yield glucose and other sugars.
Analgesia:	Absence of pain.
Analgesic ceiling effect:	A limitation of analgesic effect due to other effects of the drug. Opioid analgesics theoretically have no limit to the analgesic effects mediated by the mu receptor. However, opioids stimulate additional receptors that cause side effects that limit the maximum dose that can be given. For example, while morphine could theoretically be titrated upward indefinitely to control pain, high doses can cause respiratory depression, thus the actual maximum dose that can be given is limited by the risk of respiratory depression (and/or other side effects).
Analgesic:	Relieving pain without causing loss of consciousness, or an agent that produces the same.
Analogue:	A compound that resembles another in structure, but is not necessarily an isomer.
Anaphylaxis:	An unusual or exaggerated allergic reaction that may be life threatening.
Anatomical pathology:	The actual physical disturbances in the body. For example, a broken leg is the anatomical pathology and leg pain is the symptom.
Anesthetic:	Pertaining to loss of feeling or sensation, or an agent that produces the same.
Anorexia:	Lack of a desire to eat. (The term is similar to 'anorexia nervosa' but these are different medical conditions.)
Antagonist:	Drug that binds to a receptor site, inhibiting its action.
Anticoagulant:	Stops blood clotting, or an agent with this effect.
Anticonvulsant:	Preventing fits or convulsions, or an agent with the effect.
Antiemetic:	A drug that prevents nausea.
Antisymphathetic:	Producing effects resembling those of interruption of the sympathetic nerve supply, or an agent which does the same.
Antitussive:	Effective at relieving coughing. Antitussive effects associated with opioids are due to μ -receptor and possibly κ -receptor stimulation.
Anxiolytic:	Reducing or preventing anxiety.
Apnea:	Cessation of breathing.
Arrhythmia:	Disturbance of the heart beat or rhythm.
Arthralgia:	Joint aching.
Arthritis:	Inflammation of a joint.
Ataxia:	A lack of coordinated muscular movements that can result from neurologic disorders.
Atelectasis:	Collapse of the alveoli (tiny air sacs) in the lungs.
Atrophy:	Wasting away.
AUC:	Area under the curve. Graphically, this is the area under a drug's absorption curve. It represents the amount of drug absorbed after a dose.
Autonomic nervous system:	Part of the nervous system concerned with regulation of activity of heart muscle, smooth muscle, and glands.
Axial skeletal fusion:	Calcification of the spinal column that leads to calcified connections between the bones, leading to a loss of motion.
Barbiturates:	Group of sedatives derived from barbituric acid.

Baroreceptor reflex:	A reflex response to activation of a sensory nerve terminal that is stimulated by changes in pressure. These receptors are located in the blood vessel walls.
Baroreceptors:	Receptors that detect blood pressure.
Baseline dose:	A dose of pain medication that is given consistently to achieve an acceptable level of pain control in a given patient. The pain control is effective most of the time in most situations but may require supplementation (e.g., the pain relief is effective during both the peaks and troughs of the serum drug levels).
Bedsore:	An ulceration due to prolonged pressure from lying immobile in bed for too long (also known as decubitus ulcer).
Bile:	A greenish-yellow bitter fluid produced in the liver and stored in the gall bladder. Bile which flows in bile ducts from the gall bladder to the intestine helps in the digestion and absorption of fat.
Biliary colic:	Pain due to an obstruction (and subsequent increases in pressure) in the gallbladder or bile collecting system in the liver. This medical condition can be an adverse effect of opioid drugs. A few opioids, such as meperidine, fentanyl, and butorphanol, produce less pronounced increases in biliary tree pressure than morphine.
Biliary:	Of the bile or bile ducts.
Bioavailability:	The degree to which a drug will become available in the system after it is taken orally or injected (parenterally).
Bioequivalent drugs:	Two drugs that are similar in absorption and physiologic activity.
Biofeedback:	Process by which an individual is provided with information on the state of one or more physiological variables, such as heart rate or skin temperature; this often enables the individual to gain some voluntary control over them.
Biopsy:	Removal and examination (usually through a microscope) of tissue from the living body to establish a precise diagnosis.
Biphasic absorption pattern:	An absorption pattern of a drug that demonstrates two phases, with two distinct and separate serum drug peaks. This is seen in drug formulations in which some of the drug is released shortly after it is administered and the other part of the drug is released later.
Black box warnings:	Warnings required by the FDA for a product. They are called "Black Box" because they are required to be placed in a black box in a prominent position in the pharmaceutical information for a given drug ("package insert").
Bleeding time:	The amount of time it takes blood to clot.
Blood-brain barrier:	Selective barrier which prevents substances in the blood from entering the central nervous system.
Bolus:	large amount.
Brachial:	Pertaining to the arm.
Bradycardia:	Low heart rate.
Bradykinin:	A naturally produced substance which dilates blood vessels, constricts to smooth muscle and stimulates pain receptors.
Brainstem:	Stemlike portion of the brain connecting the cerebral hemispheres with the spinal cord; comprised of the pons, medulla (oblongata), and the midbrain.
Breakthrough pain:	Pain that occurs before the next scheduled dose of analgesic. Can also refer to episodic pain that is not fully controlled with the current pain control regimen.
Bronchial:	Pertaining to the bronchi (singular bronchus), i.e., the larger passages conveying air to the lungs.

Bronchoconstrictor:	Substance which narrows airways.
Cachexia:	General weight loss and wasting occurring in the course of chronic disease or emotional disturbance.
Carcinogenic:	Any substance producing cancer.
Carcinoma:	Malignant growth of epithelial cells.
Cardiac muscle:	Muscle of the heart, composed of striated muscle fibers.
Cardiac:	Pertaining to the heart.
Cardiogenic:	Any substances producing cancer.
Cardiovascular:	Pertaining to the heart and blood vessels.
Carpal tunnel syndrome:	Entrapment of a large nerve at the wrist, causing pain and numbness in the palm and fingers.
CAT scan:	(see Computerized axial tomography).
Catheter:	Flexible tube passed through body channels for withdrawal of fluids from or introduction of fluids into a body cavity.
Causalgia:	Burning pain, allodynia and disruption of the actions of the sympathetic nervous system in the affected region.
Ceiling affect (for analgesia):	Property of a drug, which means that further increases in dose above a certain level will not result in increases in analgesia.
Central nervous system:	Brain and spinal cord.
Central pain:	Pain that results from injury or disease in the spinal cord or brain.
Cerebral cortex:	Outermost convoluted layer of gray matter covering each cerebral hemisphere; responsible for conscious location of sensory stimuli, evaluation of sensory stimuli received from lower parts of the brain, sending instructions to muscles, organs, and glands, and intellectual processes and emotional responses.
Cerebral ventricular system:	Interconnected system of spaces within the brain filled with cerebrospinal fluid.
Cerebrospinal fluid:	Liquid which circulates around the brain and spinal cord.
Cerebrum:	Main portion of the brain, occupying the upper part of an organ (e.g., of the uterus).
Chemoreceptor trigger zone:	Region of the medulla which, when stimulated, activates the adjacent emetic center which is responsible for vomiting.
Chemotherapy:	Treatment of disease by chemical agents.
Chronic benign pain:	Pain from problems that are neither fatal nor curable.
Chronic obstructive pulmonary disease (COPD):	Condition in which irreversible damage to lung tissue, generally as a result of smoking, leads to a reduction in respiratory capacity.
Chronic:	Persisting for a long time.
Cimetidine:	A drug that reduces the production of stomach acid (also called Tagamet®).
Circulatory depression:	A reduction in the activity of the heart and normal tone of the blood vessels and can be a side effect of opioids. The clinical findings are low blood pressure and a slow pulse.
Circulatory shock:	Failure of the circulatory system to maintain adequate blood supply to vital organs.
Cirrhosis:	Progressive disease characterized by diffuse damage to parenchymal cells, especially of the liver.
Clearance:	Volume of plasma cleared of a drug per unit of time. It is a measure of the body's ability to eliminate a drug from the body.

Cmax:	Maximum concentration in the blood of a drug after dosing.
Cmin:	Minimum concentration in the blood of a drug after dosing.
Coanalgesics:	Pain-relieving agents used in conjunction with other analgesics.
Colic:	Severe, cramping, visceral pain caused by spasm of smooth muscles in the wall of hollow organs.
Compliance:	Adherence to a prescribed regimen.
Computerized axial tomography (CAT, CT) scan:	Technique which provides cross-sectional images of internal structures from information obtained by passage of x-rays through the body.
Congener:	(also spelled cogener) A substance that is chemically related to another. A member of the same kind, class, or group.
Conjugation:	This is one of the metabolic processes performed by the liver to deactivate drugs in preparation for elimination. The reaction joins a drug with another molecule to produce a form that can be eliminated by the kidney. A drug changed by this type of metabolism is sometimes referred to as a conjugate.
Constriction:	Narrowing.
Contracture:	Abnormal shortening of muscle tissue, rendering the muscle highly resistant to passive stretching.
Contraindication:	Circumstance which means a drug should not be considered appropriate treatment.
Contralateral:	On the other side.
Contrast media:	A substance which when injected into blood vessels can be seen on x-ray film. It can help define the position, size, and shape of tumors.
Controlled-release drug:	The rate at which an oral drug is absorbed depends partly on how quickly it is dissolved in and absorbed from the digestive tract. A drug can be chemically altered (e.g. the pH is altered, causing absorption to be delayed) or placed into a delivery system that alters the rate of release of the drug into the digestive tract in a predictable manner, allowing control over how quickly the drug is absorbed into the system.
Coping skill:	A means of dealing with difficult or stressful situations.
Cordotomy:	A surgical procedure involving the division of the spinothalamic tract. The spinothalamic tract contains the nerve fibers responsible for transmitting the sensation of pain up the spinal cord.
Cor pulmonale:	Heart disease which develops as a result of lung disease, leading to thickening of the walls of the chamber of the heart (right ventricle) which pumps blood to the lungs.
Corticosteroid:	A hormone produced by the outer layer (cortex) of the adrenal gland, or any synthetic equivalent; used clinically to reduce inflammation and for other purposes.
Corticotropin-releasing factor:	Hormone released from the hypothalamus which is responsible for the synthesis and release into the bloodstream of hormones from the pituitary gland.
Cough reflex:	Involuntary protective mechanism for explosively removing foreign matter or sources of irritation from the air passages of the lungs.
Counter-irritation:	Irritation or much inflammation of the skin exerted for the purpose of relieving symptoms of an inflammation of the deeper structures.
Cranial nerves:	Twelve pairs of nerves directly connected with the brain, including the nerves of sight, smell, eye movement, hearing, etc.
Craving:	An extremely strong psychological desire to use a substance.
Cross-dependence:	The "transfer" of dependence on one substance (e.g., opioid) to another.

Crossover abuse:	Shifting patterns of abuse from one substance to another, for example, an individual stops using cocaine but starts drinking heavily.
Crossover group:	Each subject is given each treatment (double crossover repeats crossover design).
Cross-tolerance:	The "transfer" of tolerance from one substance (e.g., opioid) to another.
CT scan:	(see Computerized axial tomography).
Cytochrome (CYP) P450 system:	This refers to a family of liver enzymes involved in the metabolism of various substances in the body, including drugs. The term is often abbreviated to CYP and then the number of the specific member of the family is given. These enzymes include CYP3A3/4, CYP1A2, and CYP2D6, which are involved in the metabolism of various opioids.
Deafferentation pain:	Pain which results from instability and spontaneous discharge of spinal cord nerves that have lost normal incoming sensory stimuli.
Dealkylation:	To remove a chemical alkyl group from a chemical structure. This is one way the body metabolically alters drugs into inactive forms.
Decubitus ulcer:	An ulceration of the skin caused by pressure over a bony prominence. (Bed sore)
Delayed gastric emptying:	Slow transit of stomach contents out and into the intestine. This can result from drug side effects or disease states.
Delayed release:	A drug formulation that delays the release of a drug until it has passed out of the stomach and into the intestine.
Delirium tremens:	An alcohol withdrawal syndrome that results in confusion and hallucinations. (DTs)
Demographics:	Distribution throughout the population.
Dendrite:	Extension of the neuron which receives and conducts nervous impulses towards the cell body of a neuron.
Dependence:	A state in which the usual or increasing doses of a drug are required to prevent the onset of withdrawal symptoms. A state in which a withdrawal syndrome develops if a medication is stopped suddenly.
Dermatome:	Area of skin supplied with nerve fibers from a single spinal nerve root.
Descending pathways:	Nerve fibers that travel down the spinal cord from the brain and inhibit incoming pain signals.
Detoxification:	Tapering a medication to prevent withdrawal symptoms.
Detrusor muscle:	The muscle in the bladder that contracts to initiate urination.
Diagnosis:	Determination of the nature of a cause of a disease.
Diaphoresis:	Sweating.
Dilation:	Increase in diameter or caliber.
Diplopia:	Double vision.
Disc (intervertebral):	Layer of fibrous cartilage between adjacent vertebrae.
Distention:	Swelling out by pressure from within.
Distraction:	Diversion of attention (e.g., from pain)
Distribution:	The extent of and processes by which a drug enters and remains in different areas (compartments) of the body.
Diuretic:	Increasing urine output, or agent which has the same effect.
Diversion:	The act of giving one's prescription drugs to others for their use. This may be done in exchange for money.

Dorsal horn:	Horn-shaped structure of the gray matter of the spinal cord, of particular importance in receiving incoming sensory impulses from the periphery and the transmission of outgoing motor impulses to the appropriate peripheral nerves.
Dose Titration:	Adjustment of a dose to achieve the best therapeutic response with a minimum of undesirable side effects.
Dosing interval:	The time between administration of doses.
Double blind:	Neither the patient nor the physician is aware of actual treatment.
Drug holiday:	A period during which a drug is not used to allow restoration of normal function of tissues which are adversely affected by the drug.
Drug metabolism:	The process of changing a drug from an active form to a less-active or inert form before it is eliminated from the body. This can occur by means of enzymes in the liver or the kidney.
Duodenum:	First part of the small intestine.
Dura mater:	Outermost membrane surrounding the brain and the spinal cord.
Dysesthesia:	An unpleasant abnormal sensation produced by normal stimuli or abnormal sensations experienced in the absence of stimulation.
Dyspepsia:	Impairment of the function of digestion; usually applied to epigastric discomfort after meals.
Dysphagia:	Difficulty in swallowing.
Dysphoria:	Disquiet, restlessness, anxiety.
Dysplasia:	Abnormality of development, size, shape, or organization of cells.
Dysplastic:	Pertaining to dysplasia.
Dyspnea:	Labored or difficult breathing, "breathlessness".
Edema:	Excessive accumulation of fluid in a tissue.
Efferent:	Conveying away from a center.
Elimination half-life:	The amount of time it takes the body to eliminate half of a dose of a drug that has been fully absorbed.
Embryocidal:	Causes death of an embryo in pregnant women.
Emesis:	Vomiting.
Encephalopathy:	A disease or process causing abnormalities in the tissue of the brain.
Endocrine:	Pertaining to hormones.
Endogenous:	Produced within or caused by factors within the body.
Endorphins:	General term for the endogenous opiate-like (opioid) neurotransmitters.
Enema:	Solution introduced into the rectum to promote evacuation of feces.
Enkephalin:	Endogenous opiate-like (opioid) neurotransmitter.
Enterohepatic:	Pertaining to the intestine and liver.
Enzyme:	Protein produced in a cell which is capable of greatly accelerating a chemical reaction.
Epidemic:	Affecting a large number of individuals within a population.
Epidural:	External to the dura mater, the outermost membrane surrounding the brain and the spinal cord.
Epigastrium:	The upper and midline region of the abdomen.
Epithelium:	Cellular covering of internal and external body surfaces.

Equianalgesic dose:	The dose of a given drug that is required to reach the same degree of activity as another drug. In the case of opioids, morphine is the standard used to compare potency. Doses of other opioids are often compared to morphine to determine doses that offer equivalent activity.
Equianalgesic:	Producing the same degree of analgesia.
Exclusion criteria:	Variables used to eliminate patients from the study.
Excrete:	The process of actively eliminating a molecule from inside a cell into a cavity for the purpose of removing it from the system. For example, a drug molecule may be excreted by a kidney cell into the collecting system of the kidney where it will be transported into the urine.
Excretion:	The elimination of a substance, such as a drug, from your body.
Extended-release:	A drug formulation that releases the drug over an extended period of time.
Extent of absorption:	The degree to which a dose of medication is taken up into the system from the site of administration.
Fellowship trained:	Having 1 year or more of additional medical training specifically in pain management in an accredited pain management program. The term also applies to subspecialty training of other types that goes beyond the usual residency training period.
Fibrosis:	Formation of thickened, scar-like tissue, usually as a result of injury.
Fibrous tissue:	Common connective tissue of the body, i.e., tissue which binds together and is the ground substance of the various parts and organs of the body.
First-pass metabolism:	Metabolism of a drug that occurs during its first passage through the liver in the circulation, right after absorption from the intestine.
Fixation:	Process of making immovable.
Flaccidity:	A decrease in muscle tone.
Focal:	Localized to specific areas.
Formulation:	The form a drug is in for administration. For example, an oral formulation is a form that is meant to be taken orally (by mouth).
French:	A measurement scale used for denoting the external diameter of catheters, sounds, and other tubular instruments. The scale is expressed in units, and each unit equals about 0.33mm. Thus, a 16-French catheter has a 5.3-mm external diameter (16 X 0.33mm).
Gamma knife:	Specialized machine that projects a very tightly focused beam of radiation.
Gastric emptying:	The process of the body moving the contents of the stomach into the small intestine.
Gastric stasis:	A relaxation of the stomach that causes it to not digest or propel its contents into the small intestine.
Gastric:	Pertaining to the stomach.
Gastrointestinal:	Pertaining to the stomach and the intestines.

Gastrostomy tube:	A tube inserted through a gastrostomy opening into the stomach of a patient used for feeding. It is also known as a "G-tube" or a "feeding tube." There is a small balloon on the tube that is inflated within the stomach to prevent the tube from falling out and a closed port on the end of the external section of the tube that can be opened to allow fluids and medications to be administered. Water and other fluids can be flushed through the tube from the opening of the port to clear obstruction or to make sure all the material introduced has fully passed through into the stomach.
Gastrostomy:	The creation of an opening in the stomach through which a tube is placed to allow administration of fluids, food, and medications in individuals who cannot swallow.
Genitourinary:	Of or pertaining to the urinary and genital systems.
Gland:	An aggregation of cells specialized to release materials not related to their ordinary metabolic needs.
Half-life ($t_{1/2}$):	Time required for an organism to eliminate one-half of a substance that has been introduced into it.
Hematological:	Pertaining to blood.
Hematopoiesis:	Formation of blood cells.
Hepatic:	By or of the liver.
Hepatitis:	Inflammation of the liver.
Heredity:	Genetic transmission of particular qualities or characteristics from parents to offspring.
Herpes zoster:	Reactivation of dormant chickenpox virus in spinal nerve roots, leading to blistering and severe pain (herpetic neuralgia) in the dermatome of the affected nerve root.
Herpetic neuralgia:	(see Herpes zoster). Post-herpetic neuralgia
Hesitancy:	Difficulty in starting urination.
Histamine:	Endogenous substance which has a number of activities, including dilation of small blood vessels, reduction of blood pressure, and mediation of certain hypersensitivity reactions.
Histology:	Microscopic anatomy of tissues.
Histopathology:	Microscopic anatomy or investigation of diseased cells.
Hormone:	Chemical messenger produced in the body, and carried in the blood to another organ or part which has a specific effect on the activity of certain cells or organs.
Hospice:	Organization that provides palliative and supportive care for terminally ill patients and their families.
Hydrophilic:	Literal translation is "water-loving." This refers to the ability of a chemical or agent to easily dissolve into water.
Hyperalgesia:	Abnormal sensitivity to pain that causes normal sensations to be interpreted as pain and painful sensations to be more intense.
Hypercalcemia:	Abnormally high levels of calcium in the blood.
Hypercapnia:	The presence in the blood of an unusually high concentration of carbon dioxide.
Hypercathia:	Exaggerated subjective response to painful stimuli.
Hyperesthesia:	Increased sensitivity to stimulation.
Hyperpyrexia:	Increased body temperature (fever).
Hyperreflexia:	Excessively increased reflexes.
Hypersensitivity:	State in which the body overreacts exaggeratedly to a foreign agent, e.g., a drug or chemical.

Hypertension:	Elevated blood pressure.
Hypertrophy:	Enlargement.
Hypnotic:	Produces drowsiness and/or sleep.
Hypophysectomy:	Removal of the pituitary gland.
Hypotension:	Low blood pressure.
Hypothalamus:	Part of the brain lying, above the pituitary gland; it is responsible for activating, controlling, and integrating peripheral autonomic mechanisms, endocrine activities, and many somatic functions.
Hypothyroidism:	Low levels of thyroid hormones.
Hypoxemia:	Abnormally low blood oxygen levels.
Hypoxia:	A deficiency of oxygen in a tissue.
Ileus:	Paralysis (usually temporary) of the bowels, which typically leads to constipation and abdominal distention. More severe ileus can cause nausea and vomiting as well.
Immediate-release:	A drug that is absorbed quickly after administration.
Immunity:	The body's natural defense system.
Immunocompromised:	State of impaired immunity.
Impaction:	State of being wedged in firmly.
In vitro:	Within a test tube.
In vivo:	Within the living body.
Inappropriate ADH secretion:	A syndrome in which antidiuretic hormone (ADH) is secreted abnormally.
Incidence of abuse:	The frequency that a certain drug is reported to be abused by legal agencies. Overdoses, overdose deaths, and arrests for illegal sales are the usual sources of such numbers.
Incidence:	The rate at which disease occurs.
Incident pain:	Pain that occurs in addition to a chronic-pain patient's usual pain. An example would be cancer pain that is intensified by extra physical activity.
Inclusion criteria:	Variables used to define the patient population.
Incontinence:	Inability to control discharge of urine or feces.
Indication:	Approved reason for using a drug.
Infarction:	Death of tissue that occurs when its arterial blood supply is cut off; the tissue dies because of lack of oxygen.
Inflammation:	A protective response to injury or destruction of tissues, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissues. The classical signs of acute inflammation are pain, heat, redness, and loss of function.
Innervation:	Distribution or supply of nerves to a part.
Intercostal:	Between the ribs.
Internist:	Specialist in internal medicine.
Intracerebral:	Within the brain (specifically the cerebrum).
Intracranial pressure:	Pressure within the cranium.
Intracranial:	Within the skull
Intractable:	Resistant to cure, relief, or control.

Intramuscular:	Into the muscle. This term is used for injections of medications that require administration deep into the muscle tissue.
Intranasal:	Within the nose.
Intraperitoneal:	Within the membrane of the abdominal cavity.
Intraspinal:	Within the spine.
Intrathecal:	Within the cerebrospinal fluid.
Intravenous:	Within a vein.
Jaundice:	Yellowness detectable in the skin and the whites of the eyes due to excessive amounts of bile pigments in the blood and tissue fluids. Jaundice may be the result of a liver disorder, gallstones blocking the flow of bile, or a number of other disorders.
Kappa receptor:	(also spelled κ receptor) One of the 3 major opioid receptor types in the central nervous system. This receptor is a molecule on the nerve cell that, when activated by an agonist (e.g. morphine), leads to decreased pain signal transmission. This has been named the OP2 receptor by the International Union of Pharmacology.
Kyphoscoliosis:	Deformity involving forward and sideways curvature of the spine.
Lancinating:	Tearing, darting, or sharply cutting; said of pain.
Large intestine (bowel):	The part of the gastrointestinal tract which extends from the small intestine to the anus; it includes the cecum, the colon, and the rectum.
Larynx:	Voice box.
Laxative:	Agent which promotes evacuation of feces from the bowel.
Lethargy:	Extreme drowsiness from which it is difficult to rouse an individual.
Leukocytes:	White blood cells.
Limbic area:	Primitive area of the brain which is primarily associated with the sense of smell, autonomic functions, and certain aspects of emotion and behavior.
Linear accelerator:	A machine that projects a beam of radiation.
Linear pharmacokinetics:	Having absorption and elimination properties that lead to a proportional relation between dosing and serum drug concentrations.
Lipid:	Fat or fat-like substance.
Lipophilic:	Literal translation is "fat-loving." This refers to the ability of a chemical or agent to easily dissolve in lipids, fats, or oils. These agents easily cross cell membranes, because cell membranes are composed of lipids and proteins.
Lumbar spine:	The five vertebrae (L1 to L5) in the posterior wall of the abdominal region which connect the thoracic vertebrae to the sacrum. The lumbar vertebrae are the largest vertebral bodies in the spine.
Lumbosacral:	Usually pertaining to the joint between the lowest lumbar vertebra and the sacrum, or that general area.
Luteinising hormone:	One of several hormones included in the menstrual process.
Lymph nodes:	Accumulations of lymphoid tissue along the course of lymphatic vessels; they serve as a defense mechanism by removing noxious agents from the lymph.
Lymph:	Transparent yellowish fluid collected from tissues and returned to the blood via lymphatic vessels.
Lymphatic system:	Lymphatic vessels and lymphoid tissue, considered collectively.
Lymphatic vessels:	Channels for carrying lymph back to the blood.

Lymphocytes:	Cells specialized for fighting infection and cancer.
Magnetic resonance imaging (MRI):	Technique which provides images of internal structures from information obtained by application of a magnetic field to tissues.
Malaise:	A generalized uncomfortable feeling that may be accompanied by physical discomfort.
Malignancy:	Cancer, i.e. tumor(s) with malignant properties.
Malignant:	Threatening life or tending to cause death. When referring to tumors: Having the properties of anaplasia, invasiveness, and metastasis.
Mastectomy:	Surgical removal of a breast.
Matrix:	The substances, other than the active drug, contained in a pill or capsule.
Medulla (oblongata):	Part of the brain continuous with the pons above and the spinal cord below.
Melanin:	Dark pigment of the skin, hair, and other parts of the body.
Meningeal:	Pertaining to the membranes covering the brain and the spinal cord (the meninges).
Metabolism:	1.) The physical and chemical processes essential for an organism to live, and also the transformation by which energy is made available for the use of the organism. 2.) The interactions of a drug with the body's biochemical processes. It usually results in a drug's structure and properties changing.
Metabolite:	A product of metabolism. A byproduct of a drug that has undergone chemical changes due to biochemical processes in the body.
Metastasis:	Secondary site of cancer which develops as a result of spread of cancer cells from the primary site to other parts of the body.
Metastatic tumor:	A tumor that has spread to a distant site from the original tumor.
Micturation:	Voiding of urine.
Midbrain:	Uppermost part of the brainstem, connecting the latter to the cerebral hemispheres.
Migraine:	Intense, throbbing headache, usually confined to one side of the head, caused by dilation or blood vessels in the head.
Miosis:	Constriction of the pupil of the eye.
Misuse :	Using a prescribed drug for a reason other than that for which it was prescribed or in a manner other than that for which it was prescribed.
Mixed agonist-antagonist:	Drug which acts as an agonist at one receptor but an antagonist at another.
Monoamine oxidase inhibitor:	A type of drug used to treat depression.
Morphine-3-glucuronide (M3G):	The predominant metabolite of morphine that has opioid antagonistic effects.
Morphine-6-glucuronide (M6G):	A metabolite of morphine that has analgesic properties.
Motility:	Ability to move spontaneously.
Motor:	Producing or subserving motion
Mouse micronucleus test:	This is a commonly used test that determines whether a compound is able to cause chromosome aberrations in mice. It is used to predict genotoxicity (teratogenicity) of a new drug.
MRI:	(see Magnetic resonance imaging).
Mu receptor:	(also spelled μ receptor): One of the 3 major opioid receptor types in the central nervous system. This receptor is a molecule on the nerve cell that, when activated by an agonist (e.g. morphine), leads to decreased pain signal transmission. This has been named the OP3 receptor by the International Union of Pharmacology.

Mucous membrane:	Membrane which secretes mucus, a slime composed of the secretions of glands, dead cells, white blood cells, etc.
Multimodality treatment:	Combination of chemotherapy, radiotherapy and surgery for treatment (of cancer).
Multiple group:	One or more subject groups (usually one group is a control group).
Multiple sclerosis:	Disease in which patchy loss of myelin throughout the white matter (mostly) of the central nervous system leads to weakness, lack of coordination, paresthesias, speech disturbances, and visual complaints.
Mutagenic:	An agent that increases the rate of mutation.
Mutation:	Permanent change in genetic makeup, i.e., DNA.
Myalgia:	Pain in the muscles.
Mydriasis:	Dilation of the pupil.
Myelin:	Lipid substance surrounding the axons of myelinated nerve fibers which facilitates orderly and rapid transmission of nerve impulses along the axon.
Myelopathy:	Disease or disorder of the spinal cord.
Myoclonic jerks:	Mild to moderate muscle contractions.
Myoclonus:	Spasmodic muscle contractions.
Myxedema:	A dry firm waxy swelling of the skin and subcutaneous tissues found in patients with underactive thyroid glands.
n or N:	The number of patients participating in the experiment.
Naloxone/naltrexone:	Two opioid antagonists; medications that reverse the effects of opioids.
Narcotic: (see opioid)	1.) Having the property of depressing activity of the central nervous system and, in large doses, inducing sleep. 2.) Legal term for opioid agent. 3) Abused substances
Nasogastric tube:	A tube of soft rubber or plastic that is inserted through a nostril into the stomach. This tube is used for various problems, including decompressing/draining the stomach of gas or digestive fluids if it becomes distended due to obstruction. Nasogastric tubes are of a relatively small diameter to maintain patient comfort, therefore are prone to blockage if material (e.g. medications or food) are administered through them.
Necrosis:	Death of cells, tissue or part of an organ.
Neonate:	Newborn infant.
Neoplasia:	New or abnormal growth of tissue.
Neoplasm:	Tissue formed by neoplasia.
Nerve block:	An injection of anesthetic near a major nerve. A steroid may be added to the injection for therapeutic or diagnostic purposes.
Nerve fiber:	A long, typically singular branch of the nerve cell that relays messages to and from the area it serves. These branches can be several feet long in the extremities. A fiber is also called an axon.
Nerve roots:	Paired bundles of nerve fibers which emerge at each level of the spinal cord.
Nerve tract:	A bundle of nerve axons that run together within the spinal cord or brain, functioning in a manner similar to a nerve.
Nerve:	A bundle of nerve axons (outside the brain or spinal cord) that run together within a connective tissue sheath.

Nervous system:	Organ system which (along with the endocrine system) correlates the adjustment and reactions of the body to its internal and external environment; comprised of the central and peripheral nervous systems.
Neural blockage:	(see Nerve block).
Neural:	Pertaining to nerves.
Neuralgia:	Pain in the distribution of a single injured or irritated nerve.
Neuralgic pain:	Localized pain resulting from damage to a single nerve.
Neuroendocrine system:	Collective name for elements of the nervous and endocrine systems, particularly as they interact in the control of body functions.
Neuroleptic:	Antipsychotic or psychotropic.
Neurological:	Originating from the nerves or nervous system.
Neurology:	Science of the nervous system.
Neurolytic:	Destruction of nerves.
Neuroma:	Tumor or new growth of nerve cells and nerve fibers.
Neuron:	A nerve cell, including its body and its dendrites (very short branch-like extensions of the cell body) and axon.
Neuropathic pain:	Pain which arises from diseased or damaged nerves.
Neuropathic:	Generated by the nerves. Neuropathic pain is that which is generated as a result of damage to a nerve.
Neurosurgery:	Surgery of the nervous system.
Neurotoxic:	Damaging to nerve tissue.
Neurotransmitter:	A chemical substance released from the end of a nerve cell which diffuses across a synaptic cleft to excite or inhibit a target cell (another nerve cell or an organ cell)
NMDA receptor:	A subtype of glutamate receptor on neurons. Binding with N-methyl-D-aspartate (NMDA) to these receptors opens calcium channels, allowing signal transmission (e.g. pain signal transmission).
Nociception:	The detection of noxious stimuli and transmission of information (nervous impulses) about these in sensory nerves. The perception of pain.
Nociceptive:	Relating to the perception of pain. A nociceptive receptor is a pain signal receptor.
Nociceptor:	Receptor stimulated by injury or noxious stimulus (pain receptor).
Nomenclature:	Classified system of names.
Noncardiogenic pulmonary edema:	A build-up of fluid in the lungs that is not caused by heart failure.
Nonlinear pharmacokinetics:	Having absorption and elimination properties that lead to a nonproportional relation between dosing and serum drug concentrations. This means that responses to changes in doses are more difficult to predict.
Nonopioid analgesic:	A medication that reduces pain through mechanisms other than through stimulating or blocking opioid receptors on nerve cells in the central nervous system. The mechanisms of action of various nonopioid analgesics differ. Barbiturates, such as butalbital, inhibit the gamma-aminobutyric acid neurotransmitter receptors to block signal transmission. Acetaminophen is conjugated with arachidonic acid to form N-arachidonoylphenolamine, a compound known as an endogenous cannabinoid which is responsible for its analgesic effect. Acetaminophen has also been thought to exert its analgesic effect by inhibiting prostaglandin synthesis in the brain (the prostaglandin inhibition results in a minimal amount of anti-inflammatory effect that is not clinically significant and does not contribute to the analgesic

	effect). The release of phospholipid from injured cell membranes is converted to arachidonic acid, which in turn is metabolized by a cyclooxygenase or lipoxygenase to produce prostaglandins and other chemicals that mediate inflammation. Non-steroidal anti-inflammatory drugs, such as naproxen sodium, inhibit prostaglandin production, thereby reducing pain signal transmission, and reduce inflammatory responses that contribute to pain.
Nonsteroidal:	Drugs that reduce inflammation but which are not anti-inflammatory corticosteroids agents (NSAIDs). (Nonsteroidal Anti-Inflammatory Drugs)
Noradrenaline:	Neurotransmitter and hormone; plays chief role (norepinephrine) in the transmission of information in the sympathetic nervous system, and is also a powerful blood pressure-elevating substance.
Noxious:	Hurtful, injurious.
Nystagmus:	An abnormal sideways or up-and-down movement of the eyes that is associated with neurologic abnormalities or disease of the vestibular apparatus of the ear.
Objective criteria:	clearly defined variables with exact measurements. Example: visual and numeric analog pain scales.
Occult:	Hidden, unrecognized.
Oliguria:	Diminished urine output.
Oncologist:	A physician specializing in cancer treatment.
Open label:	Both patient and physician are aware of actual treatment.
Opiate:	Alkaloids (morphine and codeine) obtained from the opium poppy plant.
Opioid naïve:	This refers to a patient who is not currently or who has not recently been treated with opioids. Opioid-naïve patients have not developed tolerance to the effects of opioids and therefore are started at the low recommended doses.
Opioid phobia (opiophobia):	Irrational fear of using strong opioids, especially morphine.
Opioid receptors:	A receptor is a group of cell membrane proteins in nerve cells that cause certain responses in the cell when stimulated or blocked by ligands. Opioid receptors are stimulated or blocked by opioids. There are different classes of opioid receptors, including delta opioid receptors (also known as OP1 receptors), kappa opioid receptors (also known as OP2) receptors, and mu opioid receptors (also known as OP3). Activation of these receptors stimulates specific activities within the activated cell, causing effects such as analgesia, nausea, or somnolence. Blockage of the effects of some types of receptors can cause effects such as anorexia or decreased prolactin release.
Opioid tolerant :	This refers to a patient who has been taking opioids and has developed physical tolerance to some of the effects of opioids, such as respiratory depression.
Opioid:	A drug that is chemically similar to or derived from opium. These drugs act at opioid receptors on nerve cells in the central nervous system to reduce transmission of painful stimuli/impulses.
Oral:	Pertaining to or by the mouth.
Oralet:	Medication in a lozenge form.
Organ:	A relatively independent body part that performs a special function, e.g., brain, liver, heart.
Orthopedic:	Pertaining to the skeletal system (bones, muscles, joints, etc).
Orthostatic hypotension:	Drop in blood pressure upon standing.
Osmosis:	Process of spontaneous movement of a substance through a membrane from a solution of higher concentration to one of lower concentration.
Osteoclasts:	Cell that breaks down bone.

Pain behaviors:	Exaggeration or magnification of the effects of pain.
Palliative:	Attempting to relieve symptoms without curing the disease.
Pallor:	Paleness.
Palpitations:	Discernible irregularities of heart beat.
Pancreas:	Large gland in the abdomen that secretes digestive enzymes and hormones.
Pancreatic duct:	Channel through which secretions from the pancreas empty into the intestine.
Pancreatitis:	Inflammation of the pancreas.
Pancuronium:	A drug used in anesthesia that paralyzes skeletal muscle.
Parallel group:	Two or more subject groups studied simultaneously.
Paralytic ileus:	A side effect of opioids that manifests as a functional stoppage of the bowel. The bowel stops all contractions in response to the drug and rather than being digested, the contents build up, leading to severe bloating, constipation, and vomiting. In rare cases of severe paralytic ileus with massive dilation of the colon, decompression with colonoscopy and selective use of neostigmine may be necessary. In select patients who cannot be treated with decompression, percutaneous endoscopic colostomy or other invasive procedures may be necessary.
Paraneoplastic effects:	Tumor-induced changes produced in tissues remote from a tumor or its metastases.
Paraspinal:	Beside the spine.
Parasympathetic nervous system:	Part of the autonomic nervous system which innervates the heart, smooth muscle, and glands of the head and neck, and the thoracic, abdominal, and pelvic viscera, usually decreasing their activity.
Parenteral:	A non-oral route of administering medicine. This includes intravenous, intramuscular (an injection), rectal suppository, or transcutaneous (through the skin, as with a skin patch).
Paresthesia:	Disordered, abnormal sensation, e.g., burning, prickling, etc.
Partial agonists:	Agents that are only partly effective as agonists. Partial opioid agonists have actions at the opioid receptors that are not as strong as agonists.
Paroxysmal:	Relating to a sudden onset of a symptom or disease, especially one with recurrent manifestations.
Pathognomonic:	Denoting a sign or symptom that is characteristic enough of a condition that it can be used to diagnose that condition.
Pathological fractures:	Fractures caused by tumor invading and destroying bone.
Pathology:	Science of disease, including the causes of disease and their effect on the structure and functions of body tissues.
Peptic:	Relating to the action of gastric digestive juices (which contain pepsin and acid).
Peptide:	A naturally occurring compound of two or more amino acids.
Peptides:	Constituents of proteins.
Percutaneous:	Performed through the skin.
Peripheral nervous system:	Nerves which connect the brain and spinal cord to the rest of the body.
Peripheral neuropathy:	Pain in the feet and hands resulting from damage to the long nerve fibers that supply the limbs.
Peristalsis:	Propulsive coordinated movements which transport food and the by-products of digestion along the gastrointestinal tract.

pH:	A logarithm scale used to measure the degree of acidity or alkalinity of a given substance. A lower pH is associated with acidity and a higher pH is associated with alkalinity.
Phantom limb pain:	Sensation, after a limb has been amputated, that the absent part is still present and painful.
Pharmacodynamics:	Describes the effects of a drug on the body and the relationship between the size of a dose and the degree of these effects. These effects would include therapeutic effects as well as side effects.
Pharmacokinetics:	A branch of pharmacology dedicated to the determination of the fate of substances (primarily drugs) administered to a living organism (usually humans). The term is derived from the greek words "pharmacon" (meaning drug) and "kinetikos" (meaning putting in motion). Specifically, this branch of study focuses on the absorption, distribution, metabolism and excretion of pharmaceutical agents.
Pharmacology:	Science of the origin, nature, chemistry, effects, and uses of drugs.
Pharmacotherapy:	Treatment of disease with medications.
Phase I reactions:	One set of enzymatic processes in the liver that metabolize drugs. Phase I reactions include oxidation, hydrolysis, and reduction.
Phase II reactions:	One set of enzymatic processes in the liver that metabolize drugs. Phase II reactions include conjugation to form glucuronides, acetates, or sulfates.
Phenothiazine:	One of a group of major tranquilizers.
Physical dependence:	State of physiological change that arises through continuous use of a drug.
Physiologic:	Originating from the physical processes of the body.
Physiology:	Science of normal functions of the body.
Piloerection:	Erection of the hair (forming "goose bumps" or "goose flesh").
PISCES:	Percutaneous Inserted Spinal Cord Electrical Stimulation.
Pituitary gland (hypophysis):	Gland situated below the hypothalamus, divided into anterior and posterior sections (lobes), responsible for the production of several important hormones.
Placebo:	An inactive substance or preparation given to satisfy the patient's symbolic need for drug therapy. It is also used as a disguise in drug studies to prevent the patient or the physician from being aware of whether the patient is on active or inactive treatment.
Plasma terminal half-life:	The amount of time it takes for the drug levels that are already present plus the drug added by a recent dose to fall to half of the peak level. This is applied to drugs for which a steady level is intermittently augmented with additional breakthrough doses.
Plasma:	Fluid portion of blood.
Platelets:	Small independent cell-like bodies in the blood that help form clots. They are actually cell fragments that break off a parent cell (megakaryocyte) and form clots by adhering to damaged tissue.
Plexopathy:	Disorder or disease of a nerve plexus.
Plexus:	Large network of nerves.
Polymer:	Compound formed by the linear combination of simpler molecules.
Polyneuropathy:	Disease process involving a number of peripheral nerves.
Polypharmacy:	Taking multiple drugs concurrently. Polypharmacy may be necessary to manage a patient's medical condition(s), however, it increases the potential for side effects and drug interactions.
Polysubstance abuse:	Abusing several different types of drugs, i.e., alcohol and cocaine and opioids, either together or at different times.

Portal circulation:	Blood vessels which collect and transport digested substances from the gastrointestinal tract to the liver.
Postherpetic neuralgia:	Pain persisting after an attack of herpes zoster.
Postsynaptic neuron:	Neuron which receives a neural impulse at a synapse.
Postural hypotension:	Decrease in blood pressure on standing.
Potency:	The strength of a drug's effects. This is not to be confused with a higher dose. A very potent drug can have powerful effects at very low doses, whereas a drug with low potency will require large doses to have any effect.
Presynaptic neuron:	Neuron which transmits a neural impulse before it interacts with another.
PRN:	An acronym made from the Latin 'pro re nata', which means as needed. It is typically used in medical orders and prescriptions.
Pro-drug:	A drug that must be metabolized by the liver before it becomes active in the body.
Prognosis:	Forecast of the probable course and outcome of a disorder.
Prophylactic:	Preventive.
Prostaglandins:	Naturally occurring compounds with a variety of actions, including some of the local effects of inflammation.
Prostate:	Gland surrounding the neck of the bladder and urethra in males.
Prostatic Hypertrophy:	Enlargement of the prostate gland.
Protein:	Complex compound which is the principal constituent of cells and which also makes up enzymes, structural elements, hormones, etc.
Protein-binding:	The property of drugs that causes them to adhere to proteins in the serum.
Pruritus:	Itching.
Pseudoaddiction:	Behaviors (that mimic addiction behaviors) exhibited by patients with inadequately treated pain.
Psychogenic pain:	Pain which arises "from the mind".
Psychological dependence:	Behavioral pattern characterized by a craving for the drug (addiction) and an overwhelming concern with obtaining it.
Psychological:	Originating from the conscious or subconscious mind.
Psychosis (Psychotic disorders):	Major mental disorders marked by derangement of personality and loss of contact with reality.
Psychostimulant:	Agent that produces increases in cerebral activity.
Psychotomimetic effects:	Side effects of drugs that affect mood and thinking.
Psychotomimetic:	Something that causes a feeling of depersonalization or dysphoria; producing symptoms similar to psychosis.
Psychotropic:	Exerting an effect on the mind.
Pulmonary embolus:	A clot or other particulate matter blocking one of the blood vessels to the lungs from the right side of the heart. The usual source of the blockage is material from a deep vein thrombosis.
Pulmonary:	Pertaining to the lungs.
Pulmonic:	Pertaining to or of the lungs.
Pupillary:	Pertaining to the pupils of the eye.
Pyloric sphincter:	Ring-like muscle between the stomach and the small intestine.

Q24h/Q12h:	Shorthand for every 24 hours and every 12 hours. Q is an abbreviation for <i>every</i> from the Latin <i>quaque</i> .
Radical:	Designed to eliminate all possible extensions of a disease process.
Radicular:	Pertaining to a nerve root.
Radiculopathy:	Disease of nerve roots which is typically painful.
Radiotherapy:	General term for all types of radiation used to treat cancer.
Randomization:	A selection procedure used to eliminate the bias in a subject population.
Receptor:	1.) A structure on the surface or within a cell that recognizes and binds with specific molecules, producing a specific effect in the cell. 2.) A sensory nerve ending that responds to various stimuli.
Recovering:	An ex-abuser who now abstains. Such individuals remain at increased risk of relapse for at least several years.
Rectum:	The final part of the large intestine, terminating at the anus.
Referred pain:	Pain felt in a part of the body which is distant from the tissues causing the pain.
Reflex:	An automatic involuntary response mediated by the nervous system.
Refractory:	Not readily responsive to treatment.
Regional anesthesia:	Nerve block which relieves pain in the area served by that peripheral nerve, nerve root, or plexus.
Relapse:	Returning to substance abuse after a period of abstinence.
Reliability:	A measure of the extent to which the experiment produces the same result.
Remission:	Temporary reduction of symptoms.
Renal:	By or of the kidney.
Rescue dose:	An additional dose of pain medication above the usual baseline dose for times when pain is worsened (e.g., when a patient with otherwise well-controlled pain overexerts himself or the disease/condition has periodic "flares" of symptoms or breakthrough pain).
Rescue medications:	Medications which the patient can take when symptoms are not controlled by the usual fixed regimen.
Resection:	Excision (cutting out) of a portion or all of an organ or other structure.
Resistance:	Natural ability of a normal organism or cell to withstand the effects of a drug that is lethal to most members of its species or to most other cells of its type.
Respiratory depression:	A reduction in the amount of respiratory effort that can be a side effect of opioids in the CNS. If this worsens, it can lead to respiratory arrest (the patient ceases to breathe).
Rheumatoid arthritis:	Chronic systemic disease, primarily involving inflammation of the joints, but also associated with disease in other organs.
Rhinitis:	Inflammation of the mucous membranes of the nose.
Rhizotomy:	Severance or disruption of a nerve root.
Sacrum:	Wedge-shaped bone in the pelvis formed by fusion of five vertebrae below the lumbar vertebrae.
Salicylate:	One of a group of drugs, e.g., aspirin, derived from salicylic acid.
Sarcoma:	Malignant tumor of connective tissue.
Scan:	An image produced using a moving detector or a sweeping beam of radiation.

Sclectrosing agent (sclerosant):	Chemical irritant injected to produce inflammation and eventual fibrosis and obliteration of a structure.
Secondary gain:	A gain (financial, emotional, or social) resulting from (or secondary to) what would appear to be an unpleasant situation.
Seizure:	Sudden attack, e.g., a convulsion (fit).
Sensory nerve:	This is a nerve that carries sensation signals, including pain.
Sensory:	Pertaining to sensation.
Serotonin:	Hormone and neurotransmitter which has a variety of properties, including inhibition of stomach secretions, stimulation of smooth muscles, and production of vasoconstriction. Also known as 5-hydroxytryptamine (5-HT).
Serum half-life:	The amount of time it takes for a drug level in the blood to decrease to one-half of the maximum amount reached. This term is sometimes shortened to "half-life."
Serum:	Clear portion of blood which remains when cells and other solid elements have been removed.
Shingles:	(see Herpes zoster).
Shock:	(see circulatory shock).
Sigma receptors:	Receptors in the central nervous system that appear to be involved in antidepressant effects and antianxiety effects. These receptors also attenuate the pain response in experimental settings, thus these receptors were originally classified as opioid receptors. They are now felt to constitute a distinct class of receptors.
Signs:	Objective evidence of disease.
Single blind:	Only the physician is aware of actual treatment.
Single group:	One subject group with one treatment.
Skeletal muscle:	Striated muscle attached to bone and crossing at least one joint; involved in voluntary activities.
Small intestine (bowel):	The gastrointestinal tract immediately following the stomach, and preceding the large intestine; comprised of the duodenum, jejunum, and ileum.
Smooth muscle:	Nonstriated muscle which is not under voluntary control.
Socio-environmental:	Originating from, or strongly influenced, social or environmental pressures.
Somatic nervous system:	Part of the nervous system which carries messages originating from the conscious part of the brain to skeletal muscles.
Somatic pain:	Sharp, localized pain originating from the skin, muscles, tendons, ligaments, and bones. This type of pain is usually well-localized and easy to describe.
Somatoform disorders:	Psychological conditions that produce physical complaints even though there is nothing physically wrong with the patient that can be identified medically.
Spasm:	Sudden involuntary muscular contraction.
Sphincter of Oddi:	A circular muscle located where the common bile duct passes through the small intestine that controls the flow of bile into the intestine.
Sphincter:	Ring-like muscle around an orifice.
Spinothalamic tract:	Group of sensory nerve fibers which transmit information from the spinal cord to the thalamus.
Spleen:	Large organ in the upper left part of the abdomen, in which old red blood cells are broken down.
Steady state:	Condition of dynamic equilibrium between administration and elimination of a drug.

Stomach atony disorder:	A condition caused by a loss of muscle tone in the stomach. It can lead to pain, nausea and vomiting, and distension.
Street value:	The price for which a drug is commonly sold for illegally (i.e., "on the street").
Stricture:	Abnormal narrowing.
Subcutaneous:	Beneath the skin. This term is used for injections of medications that require administration into the looser tissue under the skin.
Subjective criteria:	Variables that are less well defined (typically exhibiting great inpatient differences). Example: patient self-report.
Subjective:	Cannot be seen, felt, or shown on laboratory test. A subjective diagnosis is one that is made on the basis of the patient's history rather than a finding on physical exam or by testing.
Sublingual:	Beneath the tongue.
Substance abuse:	Continued use of a mood-altering substance despite repeated harmful problems associated with its use.
Substance dependence:	Substance abuse associated with tolerance and withdrawal symptoms.
Suppository:	A formulation of a drug that can be given rectally.
Supraspinal:	Occurring at the level of the brain.
Sympathectomy:	Disruption or interruption of some portion of the sympathetic nervous pathway.
Sympathetic nervous system:	Part of the autonomic nervous system which innervates the heart, smooth muscle, and glands of the entire body, usually increasing their activity.
Symptoms:	Subjective evidence of disease or a patient's condition.
Synapse:	The junction between two neurons or a neuron and an effector target organ, across which neural impulses are transmitted, usually by chemical means.
Synaptic cleft:	Narrow gap at the synapse, across which neurotransmitters are responsible for transmitting nerve impulses.
Syncope:	Fainting.
Syndrome:	A group of findings or symptoms that commonly occur together.
Systemic:	Involving the whole body.
T_{1/2}:	(see Half-Life).
Tachycardia:	Increased heart rate.
T-cells:	White blood cells primarily responsible for cell-mediated immunity.
Temporal:	The course of a situation or circumstance over time.
Tenesmus:	Ineffectual and painful straining to void feces.
TENS:	Transcutaneous Electrical Nerve Stimulation.
Tension headache:	Headache resulting from prolonged contraction of the muscles of the scalp, generally reflecting chronic stress.
Teratogen:	An agent that induces the formation of abnormalities of the fetus.
Therapeutic index:	The range of drug dose within which the drug is effective but does not cause unacceptable side effects.
Therapeutic regimen:	All of the combined treatments used for a certain condition.

Thoracic spine:	Twelve vertebrae (T1 to T12) in the chest which connect the cervical vertebrae to the lumbar vertebrae. Each of the pairs of ribs attaches to a thoracic vertebrae.
Thoracic:	Of the thorax.
Thorax:	Chest.
Thymus gland:	Lymphoid organ, located in the upper chest/lower neck region, responsible for the production and development of certain lymphocytes.
Tic douloureux:	(see Trigeminal neuropathy).
Titration:	Gradual adjustment of dose of a drug until the desired effect is achieved with
Tmax:	Time required to achieve maximum plasma concentration of a drug.
Tolerance:	The need for increased doses of medication over time to achieve the same level of pain control.
Tonsils:	Small, rounded masses of lymphoid tissue at the rear of the mouth.
Topical:	Pertaining to a particular superficial area only.
Totipotential cells:	Cells which can develop into any cell type.
Toxic psychosis:	Alterations of mental state caused by drug toxicity.
Toxic:	Poisonous.
Trachea:	Windpipe.
Traction:	Act of drawing or pulling.
Transdermal:	Through the skin.
Transcutaneous:	Through the skin.
Transduction:	Stimulation of nociceptors by noxious stimuli.
Tremor:	Involuntary trembling or quivering.
Tricyclic antidepressants:	Group of drugs used to treat depression.
Trigeminal neuropathy:	Nerve pain in the trigeminal nerve distribution (i.e., the face, teeth, mouth, nose).
Trough:	The lowest level of drug concentrations in the blood.
Tumor:	Any abnormal growth of tissue, generally a neoplastic mass.
Ulceration:	Formation of an ulcer, i.e., a local defect, or excavation of the surface, of an organ or tissue.
Ultrasound:	Mechanical radiant energy used to provide images of deep structures of the body.
Unilateral:	On one side.
Ureter:	Tube which conducts urine from the kidneys to the bladder.
Urethra:	Canal through which urine is discharged from the bladder to the exterior of the body.
Urethral stricture:	Narrowing of the passage through which urine is voided.
Urgency:	Urge to pass urine.
Urticaria:	Hives.
US Pharmacopoeia:	A legally recognized compendium of standards for drugs. It includes assays and tests for determination of strength, quality and purity.
Uterus:	Hollow female organ in which the fertilized egg develops into a fetus.
Validity:	Extent to which the experiment measures the specified objectives.
Variance:	Extent to which variables or characteristics of the subject population differ.

Vasoconstriction:	State of decreased caliber (narrowing) of blood vessels.
Vasodilation:	Relaxation of the smooth muscle in the blood vessels that results in an increase in the size of blood vessels.
Vasomotor:	Affecting the caliber of blood vessels.
Vasopressors:	Drugs that stimulate the contraction of blood vessels and therefore bring about an increase in blood pressure.
Vertebra (plural vertebrae):	Any of the 33 bones of the vertebral (spinal) column including the cervical, thoracic, lumbar and sacral vertebrae.
Vertigo:	Dizziness, specifically the type that causes a spinning sensation.
Vestibular:	Involving the inner ear organ which senses bodily equilibrium.
Viscera (singular viscus):	Any of the large internal organs, especially those situated in the abdomen.
Visceral pain:	Poorly localized pain originating from internal organs.
Visual analog scale:	A pain severity rating scale.
Volume of distribution:	A measure that describes the concentration of drug in the body tissues.